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# ENDOCRINOLOGY

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# ENDOCRINOLOGY

*THE BULLETIN of the ASSOCIATION for the STUDY of*

# INTERNAL SECRETIONS

*JANUARY–MARCH, 1920*


## THE INTER-RELATION OF THE THYREOID AND HYPOPHYSIS IN THE GROWTH AND DEVELOPMENT OF FROG LARVAE


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In attempts at establishing the function of the ductless glands, investigators are limited to relatively a few kinds of experiments. One can administer a particular gland to an animal or transplant the gland into the animal in the hope of bringing about a condition wherein the subject receives more than the normal amount of the hormone being studied. One can extirpate a gland from an animal and then administer to it preparations of the type of gland removed, and one can remove a gland of one type and administer prepared glands of another type. Still further, various combinations and modifications of the above kinds of experiments can be attempted. The unsatisfactory elements in ductless gland investigations are difficulties of controlling the experiments and the greater difficulties of interpretation of the results.

In administering ductless glands one must admit that the preparations are abnormal to begin with. The glands used are dead and only hormones that are relatively stable can be preserved. Even here we have no absolutely certain method of

*The senior author succumbed to broncho-pneumonia on Jan. 30, 1920.

checking our findings and must usually reason by inference and deduction in the interpretation of results. Further, as has previously been pointed out, experiments with prepared glandular substances are more often pharmacological than physiological, especially when extracts obtained by any agent other than physiological salt solution are used. The body itself can hardly be expected to prepare from its own glands extracts requiring strong sulphuric acid, ether, acetone, alcohol and so forth. It is one thing to bring about certain reactions by the use of such preparations and quite another to prove that similar reactions are normally brought about by the living gland within the animal's body. However, we are on reasonably safe ground when we can, by administering preparations of a particular gland, prevent the occurrence of symptoms that would otherwise result from extirpation of the gland in question.

Transplanting a ductless gland into an otherwise normal animal would seem at first sight to be a method whereby hypersecretion could be brought about and the animal thus provided with more than the normal amount of hormones from the gland in question, but a usually ignored fact is that the host exerts a controlling influence upon the transplant, as well as the transplant upon the host, so that an equilibrium often results. We have transplanted thyreoids into embryos for example (Hoskins and Hoskins '19a) and observed later that they "took," so that the animals possessed an anatomical excess of thyreoid tissue, but were apparently able to regulate the amount of thyreoid hormones secreted by their own and the transplanted glands, because no symptoms of "hyperthyreoidism" resulted.

After a ductless gland has been extirpated there is often a considerable readjustment among the other structures of the body, so that of the resulting symptoms, some are due directly to the loss of the gland removed while others are caused only indirectly by the removal, and it is usually not possible to distinguish between these categories. Metabolic processes are so complex that phenomena occurring together may be merely concomitantly and not causally related. As an example of this complexity we may consider the results of thyreoidectomy wherein there occurs a physiological (perhaps pathological) hyperplasia of the hypophysis, so that the resulting symptoms are

brought about presumably both by the thyreoid deficiency and by hyper-activity of the pituitary, and it is very difficult to tell from such an experiment the normal function of the thyreoid. At best in such cases we can only say that there is some relation between certain processes and the gland in question.

## METHODS AND MATERIAL

In the following experiments with hypophysis feeding we have administered a commercial preparation of the anterior lobe of beef pituitary (Armour & Co.) to otherwise normal larvae of Rana sylvatica, and to larvae of the same species from which the thyreoid had been removed in the embryonic stage before it could have begun to function. This preparation consists of dry substance of the anterior lobes of the hypophysis, put up in tablets of milk sugar. The tablets are composed of two grains of bovine anterior lobe pituitary substance dried in a vacuum (representing 10 grains fresh gland) mixed with three grains of milk sugar. A. C. Henderson of the Armour and Company laboratory states in a personal communication of June 4, 1919, "Our anterior pituitary substance is made from carefully selected material and is, we might say, entirely without iodin; at least there is not any more than would be found in muscle substance, which means practically none at all. It is absolutely free from thyreoid tissue."

Dr. E. C. Kendall of the Mayo Foundation, who kindly analysed this material for us, reported that each tablet of two grains of dried anterior pituitary substance contains .0035 mg. of iodine, either organic or inorganic, a content of one part in 40,000 which would be 1:200,000 in the fresh gland. Dr. Kendall is of the opinion that the iodine present is soluble, and if so, considering the amount of water in the larger aquaria, the dilution of the iodine was 1:570,000,000, a concentration much less than is necessary to stimulate metabolism in tadpoles (Swingle '19) if inorganic iodine is used.

Even if the iodine did not go into solution, only a very small fraction of .0035 mg. of it was ingested by each larva in one dose, yet in most cases an effect was noticeable within twenty-four hours after the first dose was administered.

The active principle of the hypophysis, whether it contains iodine or not, apparently is soluble, as shown by the fact that

the thyreoidless larvae continued to develop after their jaws began to metamorphose, and they were thus compelled to stop eating the tablets.

In several different experiments, most of which we have not yet described, it was found that eggs collected early in the season developed into larger animals than those taken later, or taken early and kept for a time in cold storage before being used.

In each experiment the controls and the experimental larvae were of the same age and size and were taken from the same mass of eggs.

In addition to the hypophysis tablets the experimental larvae received Spirogyra in abundance, and the controls received milk sugar and Spirogyra. The water in the aquaria was changed the day after each administration of the tablets or sugar.

The larvae were under daily observation and were measured from time to time as indicated.

Before being autopsied, the animals were fixed in Bouin's fluid.

The experiments were performed in the Anatomy department of the University of Pittsburgh.

*I. Effects of administering a preparation of the anterior lobe of the pituitary to normal larvae.*

Experiment 1. April 27, 1919.

Fifteen animals were selected for hypophysis feeding and 15 of the same size kept for controls. Each set was kept in one aquarium in which they had an abundant supply of normal food. In addition to this food, one pituitary tablet was given daily to the experimental group, while the controls received milk sugar. The treatment was continued from April 27 to May 13, 1919, making a total of 17 tablets given in this way.

Experiment 2. April 28.

Three sets of 13 animals each were chosen for this experiment. Those of the first group (A) were taken at intervals from the aquarium in which they were receiving their normal food, and placed in a small jar of water, containing one pituitary tablet. They were left in this jar for 24 hours, during which time they ate a portion of the tablet. Five treatments were

given on the following dates: April 28-29, May 5-6, May 13-14, May 15-16, May 22-23.

The second group of tadpoles in this experiment (2B) was used at first as a control for group 2A, to make sure that the effects observed in the latter were not due to the fact that the animals were temporarily deprived of their ordinary food. When group 2A was placed in the aquarium containing the pituitary tablet, group B was also taken from its aquarium and put in a small jar containing water and a few cracker crumbs. The animals were left there as long as those of group A were feeding on the pituitary substance, and then returned to the aquarium, where they received normal food. As no effect resulted from these periods of light feeding, the control was discontinued and the animals used in another way. They were left in a small jar containing water and a pituitary tablet for periods of one hour each. Nine such doses were given between May second and sixteenth.

The third group of tadpoles (C) for this experiment was composed of normal animals kept on an ordinary diet of leaves and algae.

It will be seen that in these experiments care has been taken to avoid starving the animals. In number 1, an abundant supply of normal food was always present with the hypophysis substance, and the animals ate freely of it as well as of the tablets. In 2A the effect of 24 hours at a time on light diet was checked by a control, as above described; and in 2B the periods of removal from the normal food were too short to have any effect in themselves. The effect that the sugar content of the tablets might have had was checked by the giving of milk sugar to the control larvae.

## RESULTS OF EXPERIMENTS

Experiment 1.

At the beginning of this experiment the animals measured as follows:

15 for hypophysis feeding:

Body length, 9-10 mm., average 9.4 mm.

Total length 20-23 mm., average 21.1 mm.

15 for controls:

Body length, 9-10 mm., average 9.4 mm.

Total length, 20-22.5 mm., average 20.7 mm.

The first noticeable effect of the hypophysis feeding was a marked wasting of the bodies of the animals, which gave them the appearance of starved tadpoles. As has been said, the possibility of starvation has been carefully excluded from this experiment, and this emaciation differs from that produced by starvation in the time of its appearance. A normal tadpole kept without food does not show noticeable changes in form for four or five days, and is not strikingly wasted until several days later. The emaciation following hypophysis feeding is seen within 48 hours after the experiment is begun. Within a few days, however, the animals seem to recover from the first effect of the dose, and their bodies fill out again to the normal form. While the wasted appearance of the body lasts, the animals are sluggish in their behavior. Later, however, they become more lively than the normal tadpoles, and show a high degree of irritability, so that the slightest jarring of the aquarium starts them all to swimming about very actively.

By May 3, 1919, one week after the beginning of the experiment, the measurements taken showed that the hypophysis-fed animals were growing faster than the controls. These measurements are:

Hypophysis-fed—B. 10-12 mm., aver. 10.5; total 25-29 mm., aver. 26.7 mm.

Controls—B. 9-10 mm., aver. 9.8; total 20.5-23 mm., aver. 21.9 mm.

The greater length of the tails of the hypophysis-fed animals is particularly noticeable. In them the tail made up 61 per cent of the total length, while in the normal tadpoles it was only 55 per cent of the whole.

On May 8th the measurements showed still greater difference between the two groups of animals, as follows:

Hypophysis-fed—B. 10-12.5 mm., aver. 11 mm. Total 28-36 mm., aver. 31.5 mm.

Controls—B. 9-11 mm., aver. 10 mm. Total 20.5-25 mm., aver. 22.5 mm.

In addition to the size difference, which is largely due to

the unusual length of tail, marked changes in appearance may be seen in the hypophysis-fed animals. Figure 1, drawn four days later, represents a tadpole of the average size on May 8th (Body 11 mm. Total 32 mm.) and a normal but older tadpole of the same total length is shown in figure 2. The hypophysis-fed specimen shows a decided approach to the adult form. The body has become thinner both laterally and dorso-ventrally, showing that the intestine has been reduced in length. The anal canal has also shortened, the legs are well developed, and the pigmentation is like that of a frog. All these changes show that the animal has passed its maximum size and begun metamorphosis. The normal animal of the same length shows none of these signs of approaching metamorphosis. Its intestine and anal canal have not begun to shorten, its hind legs are represented by buds of tissue, and it retains the larval pigmentation. Figures 1 and 2 also illustrate the abnormal relation of tail and body in the hypophysis-fed specimen.

On May 13th all the hypophysis-fed tadpoles in this experiment were undergoing metamorphosis. The measurements showed a decrease in length, the approach to the adult form was noticeable in all the animals, and one tadpole had three legs. Five tadpoles, all of which had passed their maximum size, were found dead on this day, and the hypoyhysis feeding was discontinued.

No fully developed frogs were obtained from this experiment, though several members of the group reached a condition just short of the frog stage. Their bodies were frog-like, but a stump of tail of a few millimeters remained. The animals seemed to have been somewhat weakened by the treatment, so that they could not survive metamorphosis. Those that reached the stage at which they were able to leave the water had undergone a great shrinkage, but died before their tails had entirely disappeared. There is, of course, a reduction of the size of a normal animal in passing from the larval to the adult stage, but it is not quite so great as that seen in hypophysis-fed tadpoles. One member of this group died on May 14, and five more on May 20. All of these had four legs, and the tails had begun to shrink. On May 25 an animal which was already leaving the water died, and on May 30 the last two were killed. One of

these, also, had practically completed metamorphosis, and was leaving the water. The other still had a considerable stump of tail.

During this time (May 13-30) the control animals had developed much more slowly and did not reach their maximum length (B. 15, total 40 mm.) until early in June. The representative normal tadpole preserved on May 20 still retains the larval form of body and the hind limbs are but slightly developed, the digits of the foot being barely distinguishable. No completely metamorphosed frogs were found until June 9th, ten days later than the day on which the last of the hypophysis-fed animals left the water. On June 17th, when the experiments were ended, one of the normal animals was practically in the frog condition, but others were no farther advanced than the hypophysis-fed animals had been on May 13.

The precocious metamorphosis of hypophysis-fed tadpoles naturally gives rise to abnormally small frogs. The first of this group to reach the adult condition is shown in figure 3, and the first control frog in figure 4 (Plate II). The hypophysis-fed animal is normal in appearance except for its size. Its length (fixed) was only 8.4 mm., while that of the normal frog (somewhat below the normal average) was 10.4 mm. (fixed). The minimum length of the other hypophysis-fed frogs from this group was 8 mm.

*Group 2A*

It was in this group that the effects of hypophysis feeding were most marked. The animals were fed for 24 hours at a time on an exclusive diet of the pituitary tablets. The toxic effect of the first dose was very noticeable. The animals became much emaciated, and floated at the surface of the water, often on their backs. They remained in this condition for several days, and although they ultimately regained their normal shape, their growth appeared to have received a check from which it did not entirely recover. There was no period when the animals of this group were larger than the controls. The disproportionate growth of the tails which was seen in experiment 1 was less marked in this group. In the interval between the first two doses (April 29-May 5) the average length of these tadpoles increased as follows: Body from 8.4 mm. to 8.8 mm.; total from

18.8 mm. to 21.5 mm. The control tadpoles, in the meantime, had grown from 8.5-18.9 to 10.5-22.4 (body and total length in mm.). The second dose, given May 5-6, had no toxic effect on the animals. Between May 6 and May 15, there was an increase of 1.2 mm. in their bodies and .9 mm. in their tails. On May 16 the effect of the feeding on the form and development of their bodies was clearly apparent. Figure 5 (Plate III) drawn at this date, is to be compared with figure 6, its control. The most noticeable abnormalities appear in the lateral view of the hypophysis-fed tadpole, from which may be seen that the intestines are already reduced, giving the animal a much smaller abdomen than is seen in the normal specimen. This shortening of the intestine is one of the later metamorphic changes in a normal animal, but occurs in hypophysis-fed tadpoles at a relatively early date, before the legs have developed to any very great extent. The legs of the animal shown in figure 5 do not correspond in their development to the condition of the intestine, but are much more advanced than the legs of the control (fig. 6), although the latter is considerably the larger of the two.

Between the dose of May 16 and that of May 22 the tadpoles increased very little in size. The average length on May 16 was: Body, 10 mm.; total, 23.6 mm.; and on May 22nd, Body, 10.5 mm.; total, 26.1 mm. This was their maximum length, and by May 26 the anal canal had shortened and metamorphosis had begun. Figure 7 shows the smallest animal of this stage of development which we obtained from any of these experiments. Although the body of this animal was only 8 mm. long, the reduced abdomen and anal canal, the well developed legs, and the pigmentation shows that it has already begun its metamorphosis.

As might be expected from the small size of the tadpoles of this group, the frogs developing from them were below the normal size. As in experiment 1, few survived metamorphosis. Those that did so range in size (fixed) from 7 to 10.5 mm., with an average length of 8.8 mm. They had an average volume of 0.15 cc. while the volume of the normal frogs was from 0.20 to 0.30 cc.

*Group 2B*

The animals in this experiment received less of the pituitary substance than those in either of the experiments just described, and the effect of the treatment was correspondingly smaller. There was no emaciation following the early doses, and the first result to be seen was a stimulation of the growth of the tail and hind legs, and the reduction of the abdomen, due to shortening of the intestine. By May 15, two weeks after the beginning of the experiment, the hypophysis-fed animals have, on the average, considerably longer tails than the controls, while the bodies remain practically the same in the two groups. The measurements taken on this date were: Hypophysis-fed: Body 11 mm., total 30.4 mm.; controls: body 10.9 mm., total 23.7 mm. Individuals may be found, however, among the hypophysis-fed animals, which show normal proportions as far as length is concerned. One of these is shown in figure 8, and is to be compared with figure 6, which represents a normal tadpole of the same length. The two show a striking contrast in outline, and in the development of their legs. Figure 8 is typical of the hypophysis-fed tadpoles at the time when the effects of the treatment are first noticeable. Comparison of this figure with figure 1 shows that although the animals of experiment 2B were stimulated by the hypophysis feeding, the changes indicative of metamorphosis took place more slowly than in the earlier experiments. Although most of the animals completed their metamorphosis early, a few showed very little effect from the feeding. An example is shown in figure 9, and its control in figure 10. The hypophysis-fed tadpole has a slightly longer tail than the normal one, and its legs are longer, but there is no external evidence of changes in the intestine. The two drawings were made on June 3, when many of the hypophysis-fed tadpoles of this group had completed their metamorphosis.

The frogs that developed from this group ranged in length from 9 to 11 mm., with an average length of 9.9 mm., as compared with the control frogs, which varied in length from 11 to 14 mm.

*Discussion of Part I.*

The effects of hypophysis feeding on normal young tadpoles may be divided into two groups: the toxic and the stimulating,

as has been noted for thyreoid feeding. To the former group belongs the emaciation which immediately follows the first dose of the pituitary substance. Abderhalden '15 noted the toxic effect of pituitary extract. This effect is temporary, and does not recur after later doses. The animals appear to acquire a tolerance for the hypophysis substance. This may be the result of the repetition of doses, alone; or it may be that larger tadpoles have a greater resistance to the toxic effect. Late in the season an attempt was made to produce this effect on a normal tadpole, in order that a figure of this stage might be drawn. No such result was obtained, however, and this suggests that a tolerance may develop normally in the tadpoles with increasing size. No emaciation was produced in group 2B, the members of which were larger at the beginning of the experiment than those of the other group. In this case, however, the dose was small, and may have failed to affect the animals on that account.

*2A.* Although these animals recovered from the toxic effect of the first dose, their growth was considerably retarded.

The more interesting results of hypophysis-feeding are seen in various indications of stimulation. The most constant of these is the relatively rapid growth of the legs and tails of the treated animals. This effect is seen in animals which have received but a small amount of pituitary substance and are apparently not otherwise affected by the treatment, as well as in those which have had so much hypophysis that their general growth has been retarded.

The early shortening of the intestine occurs in almost all the animals, although a few in group 2B were not affected in this way. This result occurs relatively much earlier in the history of the hypophysis-fed tadpole than in that of the control; and hence it is more precocious than the development of the legs.

Moderate doses of the pituitary substance cause a stimulation of the growth of the body as well as of the legs and tail.

Metamorphosis as well as growth is hastened by pituitary feeding, in proportion to the amount of the substance administered. The process takes place relatively early in hypophysis-fed larvae, so that abnormally small frogs develop, and such larvae never become as large as the size attained later by the

controls. The maximum length reached by any of our hypophysis-fed larvae was 36 mm. as compared with 40 mm. for the maximum of the controls. After metamorphosis the hypophysis-fed animals were from one-half to two-thirds as large as the control frogs, and were about three-fourths as long, as is described above.

While we do not believe that the iodine content in our preparation of pituitary was sufficient in itself to bring about the results obtained, such may be the case. But whether it is or not, the substance used was normal pituitary, and the results indicate a similarity of its action to that of thyreoid.

The normal presence of iodine in the hypophysis of mammals has been claimed by some previous investigators and denied by others. Thus Bauman '96 found no iodine in the human hypophysis, but Schnitzler '96 found a trace of it. Wells '97 reported finding 0.05 mg. of iodine in 1.22 grams of dried human hypophysis. Simpson and Hunter '09 could not find iodine in Armour and Company's ox pituitary preparation nor in the fresh pituitary of sheep following thyreoidectomy, but detected a trace in fresh normal sheep pituitary. They state that their method would detect iodine in the amount of 0.005 mg. in 1.2 grams of dried substance. Denis '11 could not find iodine in the human pituitary either before or after the administration of iodides. MacArthur '19 likewise did not find iodine in beef pituitary. Thus it appears that while iodine is present normally in the hypophysis of mammals, it may be at times either absent or in concentration too small to be detected by the technique employed.

Smith '18 states that anterior hypophysis substance and boiled lettuce fed to normal tadpoles causes a rapid growth just before the larvae begin to metamorphose and hastens this process, as compared to larvae to which liver and boiled lettuce is given. This difference in size is very much less than the variation within the two groups of larvae in Smith's experiments, and may not be of any significance. The liver may have had some effect upon the growth of the control larvae and if so they were not normal and the results obtained need confirmation. In our experiments the larvae to which anterior pituitary substance was administered began their metamorphosis before

they had become as large as larvae of this species normally grow, and as a result, the frogs which were formed are smaller than normal. Since Smith did not mention any such effect on the size of his frogs, and since he did not notice any effects in the early part of his experiments, it is evident that the preparation of hypophysis used in his experiments was different in its action from our preparation.

*II. Effects of administering a preparation of the anterior lobe of hypophysis to thyreoidless larvae.*

For this experiment twelve thyreoidless larvae were selected as shown in the accompanying table. They varied in length from 42 to 53 mm. and in volume from 0.90 to 1.45 cc. Each was placed in a separate aquarium and treated as described under "Material and Methods." They were all kept under observation from 9 to 31 days, receiving from 9 to 21 doses of the hypophysis substance.

The normal control larvae, 50 in number (see Pl. IV.) had all passed the period of metamorphosis before most of the hypophysis feeding experiments were begun. These controls grew and developed normally and do not require description. They varied in maximum size before metamorphosis from a total length of 36 mm. to 41 mm. and volume of 0.50 cc. to 0.80 cc. After metamorphosis the control frogs varied from 13 mm. to 14 mm. in body length and from 0.30 to 0.45 cc. in volume. The hind legs were about 14 mm. long before metamorphosis and 15 to 18 mm. afterwards. It is easy to tell when metamorphosis proper is beginning by noting when the anal canal begins to shorten. Skeletal changes have already begun before this time, but there is no particular point in the skeletal growth that signifies metamorphic change, since the growth of the skeleton is at first very gradual. For a recent discussion of these normal changes see Hoskins and Hoskins '19b.

Thyreoidless larvae differ from normal larvae in many particulars as Allen, Hoskins and others have already described, and only a brief description will be given here. (See Pl. IV and VI.) These larvae that have had their thyreoid removed in the early embryonic stage, grow in volume and length more rapidly than normal, but if kept in normal conditions and given normal food, will not metamorphose at least for two years, although

the control animals taken from the same eggs will change into frogs within four to eight weeks from the time the eggs are laid. These thyreoidless larvae ultimately become two to four times as large as normal larvae, but their skeleton shows little tendency to calcify or to ossify. Their legs develop only as rudimentary appendages a few millimeters in length.

It is interesting to note that Hahn '12 found four gigantic larvae occurring naturally in otherwise normal cultures of Rana esculenta, but unfortunately he did not study their thyreoids. It is highly probable, however, from Hahn's description that the thyreoids of his monsters were atrophied because the changes which he does describe are much like those occurring in thyreoidless larvae. He attributed their gigantism to hypertrophy of the pituitary.

In thyreoidectomized larvae, as in other animals, there results a hyperplasia of the pituitary after thyreoid removal, but the pituitary is not able to make good the loss of thyreoid secretions.

At the beginning of the hypophysis feeding the thyreoidless larvae resembled those previously described.

## DESCRIPTION OF EXPERIMENTS

A. (Pl. V and table.)

This larva was about twice the size of a normal larva when the feeding began, its total length being 50 mm., nose-anus length 20 mm., hind limb buds 2 mm. and volume 1.50 cc. It received 18 daily doses of one-half tablet each, only a small amount of which it ate, as described above, and was observed for 20 days.

An effect of the medication was evident within 24 hours, at the end of which time the tail had shortened 10 per cent and the volume had diminished 12 per cent. The animal had become more active, as was true in all the following experiments after a single dose of hypophysis. If one approached or touched the aquaria, the larvae swam rapidly about and were difficult to catch, whereas before the medication began they were rather unresponsive to ordinary stiumli. The same effect was produced by Smith '16 by extirpating the hypophysis.

After two days the tail of animal A had decreased an additional 9 per cent in length, the volume had decreased 3 per cent,

and the hind limbs had lengthened 25 per cent.

Between the sixth and eighth days the anal canal disappeared, the animal's body now being 17 mm. long.

Between the fourth and twelfth days the tail underwent a secondary growth period, giving the animal a total length of 48 mm. The hind limbs had grown to 15 mm., which is the average leg length of young frogs. The volume had, during this period, decreased to about two-thirds of the original. On the thirteenth day the left foreleg broke through the operculum. By this time the shape of the body and head was definitely that of a frog. The pigmentation and other skin changes also were those of normal metamorphosis. Two days later the other foreleg appeared. It came through the toughening skin with considerable difficulty. On the seventeenth day the total length was reduced again to 44 mm. The tail did not, however, have the appearance of a normal larval tail of the same length, being but half as wide dorso-ventrally and half as thick, showing evidence of impending disappearance. The body was still 17 mm. in length, but had become very much thinner. The hind limbs were 20 mm. long, were somewhat disproportionately thick, and were short also in relation to the size of the body. The volume was not measured at this time, but it appeared to be further decreased.

On the twentieth day of the experiment the animal was found dead in its aquarium, too much swollen for accurate measurement. It was much larger than a normal young frog, as was to be expected from the size of the larva at the beginning of the experiment. The animal had the shape and pigmentation of a frog, but a long narrow tail still persisted.

Autopsy showed the gastro-intestinal tract to be almost completely metamorphosed, the liver being greatly reduced in size and the gall-bladder enlarged as occurs normally; the gills were small and the lungs well differentiated, as were the kidneys, gonads and brain. In general it may be said that metamorphosis was between 80 and 90 per cent completed.

A. A. (Pl. V, VI, and table.)

At the beginning of the experiment the total length of this larva was 42 mm., the body length 19 mm., the hind limb buds 2 mm., and the volume was 0.98 cc. It was thus about a third

larger than the average of the control larvae. It received 15 half-tablet doses of the pituitary substance during the first 18 days of the experiment, and was kept under observation for 31 days. In the first four days the tail increased 3 mm. in length, but the volume decreased to 0.75 cc., a loss of about 23 per cent, due partly to expulsion of intestinal contents.

By the sixth day the length had not changed, but the hind limbs had doubled in length and the volume had increased very slightly. By the ninth day the anal canal had shortened 3 mm., the hind legs had grown another mm. and the volume had decreased to about 66 per cent of the original.

On the next day the nose-anus length had still further decreased to about 74 per cent of the original and the hind legs had increased to 5.5 mm. On the twelfth day the total length was 41 mm., but the tail was very narrow dorso-ventrally, the volume had increased to 0.75 cc., the hind limbs were 6 mm. and the pigmentation was changing toward that of a frog.

Three days later the tail had increased 1 mm. and the hind limbs 3 mm., and the head and body were changing in shape toward that of a frog. On the nineteenth day the animal looked like a frog except for its long narrow tail. Both forelegs had appeared. The medication was stopped at this point.

Three days later the tail had shortened by 3 mm., the body length had increased 1 mm., the hind limbs were 16 mm. in length and the volume had been decreased to 51 per cent of the original. On the twenty-seventh day the tail had shortened again by 3 mm., and the hind limbs had increased in length another mm. The larva frequently tried to protrude its head from the water, so it was placed in an aquarium one end of which contained shallow water. From this time to the end of the experiment the animal, unless disturbed, remained in this end of the aquarium with its head out of water. On the thirty-first day the animal, which had practically become a frog, still had a very narrow and thin tail 20 mm. in length. Its volume had decreased to 36 per cent of the original, a decrease equal to the maximum loss suffered by a normal larva during metamorphosis. On this day while being examined it jumped from the observer's hand and was killed by the fall.

Autopsy showed a fully differentiated gastro-intestinal tract,

the liver being even smaller than that of normal frogs, and the gall-bladder rather larger than normal. The gills had not been reduced in size as much as occurs in normal metamorphosis, although the lungs were well developed and functional. The kidneys appeared normal, the ovaries were quite large, and the brain was as fully differentiated as that of a young frog. Metamorphosis seemed to be complete save for the fact that the tail had not fully disappeared and the gills had not been very much reduced in size.

B. B. (Pl. V and table)

This animal had received but three doses of 2 grains each when it died on the fourth day. The total length had been reduced 4 per cent, its body length 7.5 per cent and its volume 33 per cent. Since the animal when measured on the previous day was almost as long as when the experiment began, it may have shrunken between the time it died and the time it was removed from its aquarium. A part of the loss in volume was due to discharge of fecal matter. At autopsy the viscera were still in the larval condition.

B. (Pl. V and table.)

This larva received eight daily doses of 1 grain and on the ninth day while being anaesthetized to be drawn, it died and was fixed. An effect of the pituitary substance was noticeable twenty-four hours after the experiment began, when it was seen that the entire length had changed from 46 to 47 mm., the body length from 20 to 20.5 mm., the hind limb from 1.5 to 2 mm., all signs of growth, but the volume had decreased from 1.30 to 1.15 cc.

On the next day the animal was the same length, but its volume had decreased to 1.10 cc. and the hind limbs had increased to 2.5 mm.

On the fourth day the tail had lengthened another mm., and the hind legs 0.5 mm., but the anal canal had decreased 1.5 mm., and the volume 0.10 cc., the latter being now 23 per cent less than at the beginning of the experiment. By the seventh day the anal canal had disappeared and the body was beginning to change in shape. On the ninth day the larva had decreased in total length to 47 mm., and in nose-anus length to 16 mm.

The volume was 0.85 cc. or about 65 per cent of the original. The hind limbs had grown to 7 mm. and the fore limbs beneath the operculum were 3.5 mm. long.

Autopsy showed that the gastro-intestinal tract was changed about half way to that of the frog stage. The liver had formed its three lobes, was being freed from the coil of gut which in the larval stage is embedded in it, and the gall-bladder had increased in size. The gills showed little change, but the lungs were large and air-containing. The kidneys and ovaries showed no peculiarities. The latter were large, but as Allen and we have shown, thyreoidless larvae develop large gonads. The brain showed differentiation beyond that of the thyreoidless larval type.

C. (Pl. V and table.)

This animal reacted in about the same way as A. It received 18 one-half tablet daily doses of the anterior pituitary substance and was found dead in the aquarium on the twentieth day, from drowning or other cause.

Within 24 hours after the first dose the larva began to decrease in volume. As in most of the experiments the tail increased in length at first, but rapidly decreased in size, and after 10 days, in length also. On the tenth day the total length was still 1 mm. greater than at first, but the nose-anus length had lessened by 24 per cent from shortening of the anal canal and the volume had decreased by 44 per cent. The hind legs were now 8 mm. long.

On the seventeenth day the total length had decreased to 40 mm. and the body length to 15 mm. The hind limbs were 13 mm. long and the left foreleg had broken through the skin. The volume was not measured, but was seen to be less than before. The shape of the head and body and the pigmentation were definitely those of a frog, and the mouth and jaws also had metamorphosed. The skin had become toughened to such extent that the right foreleg could not break through it, and on the next day a small incision was made in the skin to release this leg.

On the twentieth day the animal, a frog to all intents and purposes except for a narrow tail of 30 mm., was found dead. It was somewhat swollen, so the volume could not be taken, but

the animal had decreased in size more than the average normal larva during metamorphosis.

Autopsy showed that the viscera were nearly completely metamorphosed, as in animal A. The kidneys and liver were especially small. The ovaries were large and the brain well differentiated. The other viscera also were those of a normal young frog.

D. (Pl. V. and table.)

This larva received 13 doses of pituitary substance, and reacted about the same as did larva C., but somewhat more rapidly, and in seven days its metamorphosis was further advanced than that of the other. Its volume by this time had been reduced by a third, its nose-anus length by a fourth, and its hind legs had lengthened to 5 mm.

By the twelfth day the total length and volume were rapidly decreasing, the hind legs were 13 mm. long and one foreleg had appeared. As in animal C, the other foreleg had to be liberated by operation because the skin had toughened, and like animal C, this animal was found dead in the aquarium two days later.

At autopsy its viscera were seen to have metamorphosed to the same extent as in animal C, except that the gastro-intestinal tract was not quite so completely differentiated, and the gills were somewhat further reduced in size.

E. (Pl. V and table.)

This larva received 21 one-half tablet doses and reacted as did D. In nine days it lost 45 per cent of its volume, its tail decreased in size and its head and body began to resemble those of a frog. In twelve days one foreleg broke through the skin and a few days later the other appeared. By the seventeenth day, except for a narrow tail the animal appeared quite like a frog. By the twenty-second day the volume was down to 40 per cent of the original, the hind limbs were 12 mm. long, the tail was still present but was becoming smaller and the body was fully reduced to the size, shape and color of a frog. The thin ventral and dorsal fins of the tail had nearly disappeared, giving this appendage a near-rod shape.

Autopsy showed a completely metamorphosed gastro-intes-

tinal tract, including a very small liver and very large gall-bladder. There were small gills, large air-containing lungs, small kidneys, large spleen, spherical and well differentiated testes and a well differentiated brain.

F. (Pl. V, VI and table.)

This animal received 15 half-tablet daily doses, and it reacted very rapidly to the medication. There was at first an increase of 2 mm. in the length of the tail, but a decrease in the volume of the body. In five days the volume decreased from 0.93 cc. to 0.80 cc., the legs grew from 2 to 7 mm., and the anal canal shortened 2 mm. The body during this time had become slender from discharge of fecal contents and from contraction and shortening of the gut. By ten days these changes had gone on still further, and the animal had the general shape and color of a frog.

By the fifteenth day one foreleg had appeared, but the tough skin seemed to have prevented the appearance of the other. Except for this, and the presence of the tail, the animal resembled a fully formed frog. The tail had begun to shorten and its dorsal and ventral fins had almost completely disappeared. The volume of the animal had decreased to 60 per cent of the original, and the hind limbs had lengthened to 18 mm.

At autopsy were found a practically differentiated gastro-intestinal tract, gills that had decreased somewhat in size, lungs that were very large and full of air, small heart and kidneys, spleen and ovaries well developed, and brain fully metamorphosed.

G. (Pl. V and table.)

This large thyreoidless larva was kept in this group of animals to serve as a control and was fed algae and milk sugar, although such procedure was not really necessary since Allen, Hoskins and others have shown that thyreoidless larvae retain the larval condition under normal circumstances, and as shown in section I of this paper, milk sugar alone has no direct effect upon metamorphosis. This animal (G) was kept for 15 days in a dilute sugar solution and fed on algae. It continued to grow, but showed no signs whatever of metamorphosis. Its growth was somewhat more rapid than that of average thyreoid-

less larvae of the same age kept on a normal diet, but was little if any more rapid than the maximum growth of such larvae.

At the end of the experiment this animal had increased in total length from 47 to 52 mm., including an increase in body length of 3 mm. The volume had changed from 0.98 to 1.40 cc., a growth of 43 per cent as contrasted with a decrease in volume of 30 to 60 per cent suffered by the other larvae. This animal was thus from two to three times as large as the larvae that had received 15 doses of pituitary substance.

Autopsy showed its viscera all in the larval condition as previously described for thyreoidless larvae (see Hoskins and Hoskins '19b). The brain was especially small and undifferentiated, whereas the ovaries, which are not retarded by thyreoidectomy, were well developed and contained oöcytes visible on the surface of the gonad.

H. (Pl. V and table.)

This animal received 9 daily 1 grain doses of the anterior pituitary substance, and reacted about the same as the other thyreoidless larvae after the same amount of medication. The length decreased slightly, the anal canal disappeared, the volume decreased about a third and the hind legs grew to 10 mm. The animal was then killed, fixed and autopsied. The forelegs under the operculum were 4 mm. long. The shape of the body and the pigmentation of the skin were changing to those of a frog. The mouth had just begun to change. The stomach was being formed, the gut was shortened to about half the larval length, the liver was still large, but had formed its three lobes and was decreasing in size, having freed itself from the coil of gut formerly embedded within it. The gall-bladder had enlarged. The gills were still large, but the lungs were fully expanded and air-containing and the kidneys had decreased in size. The testes were spherical and well developed, and the brain was about half way between that of a larva and a frog.

I. (Pl. V, VI and table.)

This larva also received nine doses of the preparation and reacted about the same as did H, except that its loss in volume (55 per cent) was greater, and its tail became relatively smaller. Its leg growth was relatively the same as that of H.

At autopsy its liver, stomach, kidneys, lungs and spleen were found to be completely metamorphosed. The intestine was about three-fourths reduced to the frog type, the gills were slightly reduced, and the brain had become nearly differentiated.

J. (Pl. V, VI and table.)

This animal was treated similarly to I and reacted in the same manner, except that its loss in volume (35 per cent) was not so great.

The viscera were in practically the same condition as those of I.

### DISCUSSION OF EXPERIMENTS OF SECTION II

In the above experiments it was noted that in most cases the length of the animal increased slightly during the first day or two of the hypophysis feeding, before involution began. In one case (AA) this added length persisted for ten days, although in this, as in other cases, the volume of the tail was steadily decreasing regardless of length, because of a shrinkage both dorso-ventrally and laterally. In this involution the tail did not react quite the same as it does in natural metamorphosis, the muscles and cartilage being more resistant than the skin and connective tissue.

The volume began to decrease in every case within twenty-four hours, and in all but one experiment, the decrease was continuous. A considerable portion of this loss in the first few days was due to discharge of feces, as occurs naturally with the shrinkage of the gut. The total loss in volume suffered by the larvae was quite as extensive as occurs naturally, being 63 per cent in one case.

One animal (AA) continued to metamorphose for thirteen days after the medication was stopped, indicating either that the absorbed pituitary substance persisted for some time in the larva or else that it had started some process within the animal that was able to continue after the intake of pituitary ceased. In all of the cases in which the jaws of the larvae began metamorphosis (AA, A, C, D, E, F) the animals quit eating the pituitary substance and could have been influenced after that time only by the extract soluble in the water of the aquarium

or else by a persisting effect of the substance eaten previously. The animals' ceasing to eat the tablets may account for the failure of their tails to disappear entirely.

The effect of the medication on the viscera was evident earlier than the effect on the somatic structures so far as macroscopic changes could be noted. There occurred on the first day the decrease in the size of the abdomen referred to above and the anal canal began to disappear usually within three or four days, being entirely gone, in some cases, in five days.

At autopsy the viscera were found, in every case, to be further advanced in metamorphosis than were the somatic parts as a whole, although the skeletal development was well advanced. The gastro-intestinal tract differentiated fairly early, being nearly half completed in nine days. The shrinkage of the liver that occurs normally during metamorphosis was very marked in these experiments, in one animal (E) becoming actually smaller than the gall-bladder. The gonads which are not directly affected by metamorphosis resembled those already described for thyreoidless larvae. The kidneys and spleen underwent their usual metamorphic changes in most of the animals of these experiments, but the gills tended to persist for a longer time than they do in normal metamorphosis. The lungs are not affected directly either by thyreoidectomy or natural metamorphosis, as we have shown in a previous publication, and there was no effect on them in these experiments. In all cases they were noted at autopsy to be expanded and to contain air, but this is true also of the lungs of undifferentiated larvae. The brain, which in thyreoidless larvae develops much more slowly than normally, was markedly stimulated in its growth by the hypophysis feeding, and after but nine doses given to animal I, for example, the brain had changed almost completely to the shape found in young frogs.

The skeleton, as indicated by the growth of the legs, showed considerable variability in its response to the pituitary substance. Animal F (Pl. V) developed a larger skeleton in a shorter time than did E, although at the beginning of the experiment it was the smaller of the two animals. The skin developed in some cases more rapidly than did the legs, and in C, D and F the right foreleg was unable to break through it.

The action of the pituitary substance in these experiments was somewhat less extensive and less rapid than has previously been described for the thyreoid in experiments of the same kind.

## GENERAL DISCUSSION

It has been believed for many years that the thyreoid and hypophysis are able, to a certain extent at least, to function vicariously. This idea was expressed by Rogowitsch '89, who noted hypertrophy of the hypophysis in rabbits, following thyreoidectomy, an experiment probably first performed by Raynard '34 and repeated since by a very large number of other investigators. In cases of pregnancy (Paton '13) and in naturally occurring myxoedema, there has also been noted pituitary hypertrophy (Boyce and Beadles '93). Ascoli '12 has shown, on the other hand, that after removal of the hypophysis of mammals the thyreoid tends to atrophy, and Adler '14 and others have verified this finding in the amphibia. In addition to the above mentioned effects of removing either the hypophysis or the thyreoid, many other changes have been described for other organs and tissues, and changes in either the thyreoid or hypophysis can be produced by experiments other than removal of one of them. Livingston '14, for example, noted hypertrophy of the pituitary after the spaying of rabbits. Jackson '17 found that the hypophysis of rats decreases in size during inanition; Cushing and Goetsch '15 described a similar decrease in the pituitary of woodchucks during hibernation; in both cases the hypophysis returned to normal when the animals were given a normal diet.

The effect on the hypophysis of thyreoidectomy in mammals has been seen since the experiments of Rogowitsch '89, by Hofmeister '94 and more recently by various workers (see Vincent '12, Biedl '13, or Paton '13). Viguier '11 obtained the same effect in lizards, and Hoskins and Hoskins '18, Rogers '18 and Larson '19 have noted it in amphibia. Hence the relationship between the thyreoid and the hypophysis indicated by this kind of experiments probably obtains in all classes of animals.

Response to feeding thyreoid substance has been investigated in many kinds of animals and with fairly uniform results. When large doses are administered the animals are poisoned, but when properly regulated amounts are used there occurs a

stimulation which, however, has been interpreted differently by different investigators. This effect in mammals has recently been discussed by Hoskins '16, Herring '17, and Kojima '17, and in protozoa by Shumway '17. The classic studies of Gudernatsch '12, '14, have shown the remarkable stimulating effect of thyreoid extract when fed to amphibian larvae. Morse '14 found the action to be due to the iodine content of the thyreoid. He was unable to obtain it with inorganic iodine, but did obtain it with iodized blood albumen. Lenhart '15 stated that the effect on frog larvae was proportional to the iodine content of the thyreoid substance used, but he also was unable to get the same results with inorganic iodine. Lenhart pointed out further that the effect in hastening metamorphosis was of a general nature and not due to any specific differentiating property of the thyreoid. Romeis '15 using Lugol's solution likewise was unable to bring about precocious metamorphosis of frog larvae by administering inorganic iodine. Abderhalden '15 showed that the result could be obtained with thyreoid substance thoroughly digested and later, Swingle '18, repeating the experiments with iodine, was able to stimulate metamorphosis in normal frog and toad larvae and in those which had had their thyreoids removed. He hastened metamorphosis in frog larvae with M/1,100,000 iodine solution ('19). Allen '19 produced the same kind of stimulation in amphibian larvae which had had both the thyreoid and hypophysis extirpated.

From the above experiments, and especially from the work of Kendall '19, it seems highly probable that the active principle in the thyreoid is some iodine compound, and, as far as amphibia are concerned, inorganic iodine appears to be as capable of markedly stimulating metabolism as thyreoid substance itself. There are possibly various other organic and inorganic substances able to produce the same effect, if, as Kendall points out, it is simply in the nature of catalysis.

Experiments with the hypophysis are by no means so uniform in their results as are those with the thyreoid. There is an admitted relation of the hypophysis to carbohydrate metabolism as discussed recently by Keeton and Becht '19, and to skeletal and other growth (Cushing '12), but the exact details of these relationships are still in dispute. In higher animals, re-

moval of the hypophysis (Cushing '12) is incompatable with life, although larval frogs are able to live without it (Adler '14, Smith '16 and Allen '16, Hoskins and Hoskins '19a), and Houssay '17 was able to keep alive some adult frogs from which the hypophysis had been removed.

From 1897 to 1916 there was about an even division of opinion as to whether pituitary feeding would or would not give positive results (for discussion see Schiff '97, Biedl '13, and Hoskins '16), but since then most of the papers published on the subject agree that at least with the feeding of the anterior lobe of the hypophysis, a definite stimulation of growth can be produced. This has been claimed for protozoa (Flather '19), worms (Wulzen '16), birds (Winternitz '16, opposed by Pearl '16) and mammals (Robertson '17 and Marinus '19). Numerous other papers on the subject will be found abstracted in the files of Endocrinology, 1917-20.

Massay '08 tried to prevent the usual symptoms following thyreoidectomy of dogs, by hypophysis-extract injections, and obtained negative results. Larson '19 with somewhat similar experiments reports that these symptoms can be prevented from occurring in thyreoidectomized rats by hypophysis feeding, but Allen '19a, states that he obtained negative results when he administered beef pituitary substance to thyreoidectomized tadpoles. As described above, anterior pituitary substance will bring about almost if not complete metamorphosis of thyreoidless frog larvae.

As to the effect of feeding hypophysis substance to normal tadpoles, Gudernatsch '12, '14, reported negative results with hypophysis extract carried from New York to Vienna and kept in the laboratory at room temperature. Abderhalden '15 performed a few experiments with an extract of thoroughly digested hypophysis substance and found it very toxic to his tadpoles, but noted that in a few cases it seemed to stimulate their development. He regarded his results as indefinite. Smith '18, states that anterior pituitary substance stimulates growth of frog larvae just before metamorphosis and then hastens this process.

That we were able to bring about early metamorphosis in normal frog larvae by the administration of anterior pituitary

substance is not surprising, in view of the fact that hypophysis substance has previously been shown to stimulate metabolism and the fact that such stimulation is sufficient in itself to hasten metamorphosis of amphibians. As Lenhart '15 pointed out, in the numerous experiments wherein early metamorphosis of tadpoles has been induced, what really occurs is simply the hastening of a natural process. Nothing fundamental takes place during this hastened change of form that does not happen naturally at a lesser rate.

Concerning the manner of action of pituitary substance fed to animals, we have no certain explanation. We cannot as yet determine whether the action upon the metabolism is direct or whether the substance acts by stimulating some gland or other structures of the body. It is doubtful whether the influence of the hypophysis fed to normal tadpoles is exerted entirely upon the thyreoid because, as we described above, the same sort of phenomenon is seen when this substance is administered to larvae which have been deprived of their thyreoids. Moreover, the action is not simply a stimulation of all general metabolic processes, because thyreoidless larvae will live for months or years on a normal diet without undergoing metamorphosis, whereas they begin to metamorphose within twenty-four hours if anterior pituitary substance is administered to them. The hypophysis of these thyreoidless larvae has undergone a distinct hyperplasia, apparently in an attempt to make up the deficiency of thyreoid secretion, but it is not successful, and in these experiments the pituitary preparation may act through the animal's own hypophysis. Smith '18 was unable to cause metamorphosis of hypophysectomized larvae by hypophysis feeding, but as Allen '19b shows, larval amphibia which have been deprived of both thyreoids and hypophysis go nearly, if not completely, through metamorphosis if inorganic iodine is administered to them. But it is also true that the normal larvae in our experiments reacted more completely to pituitary feeding than did those which were without thyreoids, and more completely than did Allen's larvae which were without both thyreoids and hypophysis, react to iodine. Hence it seems probable that when the thyreoids and hypophysis are present their activity during metamorphosis is augmented by the administration of thyreoid, iodine, or pitu-

itary, and in the absence of one or both of these glands, the above mentioned substances are able to supplement their activity to a considerable extent. It is quite possible that Allen's larvae and our thyreoidless larvae failed to metamorphose completely because of the fact that when their jaws metamorphose they cease eating the administered substances. Swingle '19, however, caused normal and thyreoidless larvae to metamorphose by placing them in a dilute solution of iodine, so it is probable that this halogen is absorbed in quantities sufficient to produce the effect noted. It has long been known that the skin of amphibia is pervious to substances soluble in water.

In the metamorphic processes produced in thyreoidless larvae by pituitary feeding, there was some variability of the minute details of these phenomena as described above. In some larvae the skeletal growth was relatively more rapid than in others, and the changes occurring in the different viscera were variable, the entire process not being quite so well co-ordinated as in normal metamorphosis.

Finally, as stated in the introduction, the results obtained by feeding preparations of dead ductless glandular substances to animals may be pharmacological rather than physiological, and may not represent the normal functions of the animal. This is certainly true of feeding inorganic substances such as iodine.

## SUMMARY AND CONCLUSIONS

We have found that a preparation of the anterior lobe of beef hypophysis, which contains some form of iodine, 1:200,000 of fresh substance, when administered to normal frog larvae will bring about a precocious metamorphosis, resulting in the production of frogs the size of which varies with the size of the larvae at the beginning of the experiment. If the original larvae are very small, they never become as large as the controls and the resulting frogs are small. Such frogs have little vitality. If permitted to remain exposed to the air they die and dry down almost flat, losing their shape, and there remains but a very small percentage of the original volume. We have not yet studied these small frogs microscopically, but they appear to have a relatively high water content. Pituitary substance is more toxic to small than to larger larvae.

When the pituitary preparation was administered to thyreoidless larvae which would otherwise have remained in the larval form more or less indefinitely, a beginning of metamorphosis occurred within twenty-four hours; it progressed somewhat more slowly than in the other experiments just mentioned; but it ultimately became nearly complete by the time the animals were either killed or died spontaneously.

From these experiments the hypophysis, in its relation to amphibian metamorphosis, is to be ranked with the thyreoid as shown by the well known work of Gudernatsch.

We regard the results obtained as due to a stimulation of natural general metabolic processes, either directly or indirectly, but the exact nature of this action is not known. The effect is both progressive, as seen especially in the skeletal and cutaneous development, and retrogressive, as seen especially in the digestive tract and tail.

It is very doubtful that the action of the anterior pituitary substance is due merely to its iodine content, although such may be the case. Other tissues with traces of iodine will not produce the same effect as the pituitary.

It is quite possible that the initial stimulation in hypophysis feeding is exerted upon the calcium and phosphorus metabolism as is indicated by skeletal changes in these experiments, although intestinal transformation also begins very early.

The hypophysis and the thyreoid are closely related physiologically and can to some extent function vicariously.

Recent investigations by various workers with amphibian larvae have developed the following facts concerning the thyreoid and hypophysis:

1. Removal of the thyreoid hastens growth, causes hyperplasia of the hypophysis and prevents metamorphosis.

2. Removal of the hypophysis retards growth, retards development of the thyreoid, prevents metamorphosis, and retards development of cutaneous pigment.

3. Feeding thyreoid or hypophysis (or iodine) to normal larvae hastens metamorphosis.

4. Feeding thyreoid or hypophysis (or iodine) to thyreoidectomised larvae brings about metamorphosis.

5. Feeding hypophysis to hypophysectomised larvae stimulates growth but does not cause metamorphosis.

6. Feeding iodine to larvae with both the thyreoid and hypophysis removed causes metamorphosis.

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PLATES I to VI

TABLE

## PLATE I.

Fig. 1. Hypophysis-fed tadpole. (Ex. 1) 15 days after beginning of experiment. Body 11 mm. Total 32 mm. X 2.

Fig. 2. Normal tadpole. Body 13.5 mm. Total 32 mm. X 2. Both drawn from the living animal.

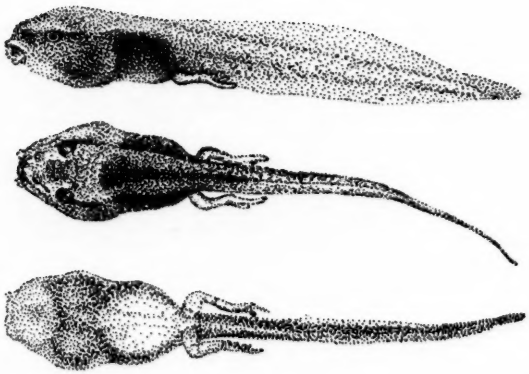


Fig.1

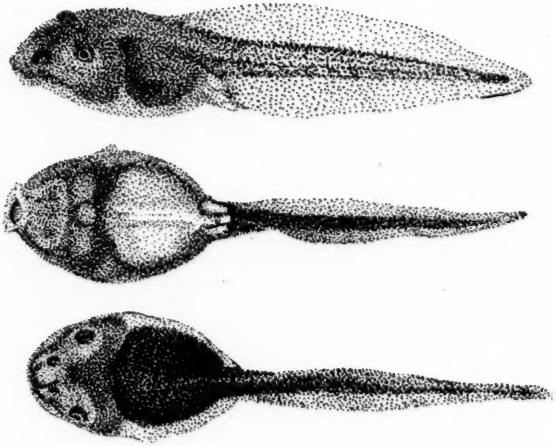


Fig.2

## PLATE II.

Fig. 3. Hypophysis-fed frog. (Ex. 1.) 28 days after beginning of experiment. Body 8.8 mm. X 2. Drawn from the living animal.

Fig. 4. Normal frog. Body (fixed) 10.4 mm. X 2.

Fig 3

Fig 4

PLATE III. All drawn X 2 from the living animals.

Fig. 5. Hypophysis-fed tadpole (2 A) 18 days after beginning of experiment. Body 9.5 mm. Total 21 mm.

Fig. 6. Normal tadpole. Same age as above. Body 12 mm. Total 28 mm.

Fig. 7. Hypophysis-fed tadpole (Ex. 2 A) 28 days after beginning of experiment. Body 8 mm. Total 21.5 mm.

Fig. 8. Hypophysis-fed tadpole (Ex. 2 B) 13 days after beginning of experiment. Body 12 mm. Total 28 mm. Compare with Fig. 6 for tadpole of same length.

Fig. 9. Hypophysis-fed tadpole (Ex. 2 B) 31 days after beginning of experiment. Body 15 mm. Total 35 mm.

Fig. 10. Normal tadpole. Same age as in Fig. 9. Body 15 mm. Total 33 mm. (Later the controls became larger than the hypophysis-fed larvae.)

Fig. 5

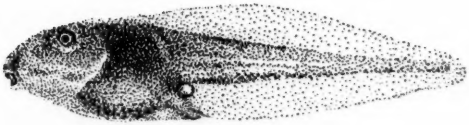


Fig. 6

Fig. 7

Fig. 8

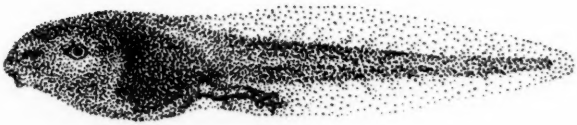


Fig. 9

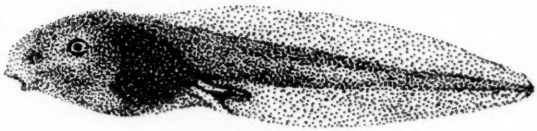
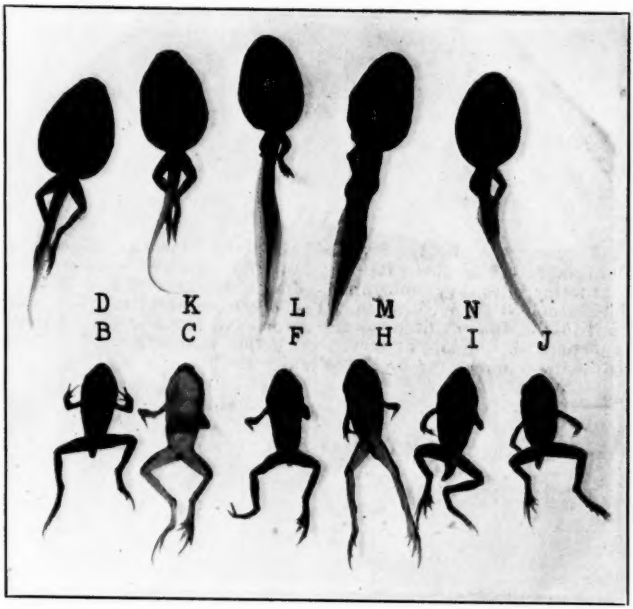


Fig. 10

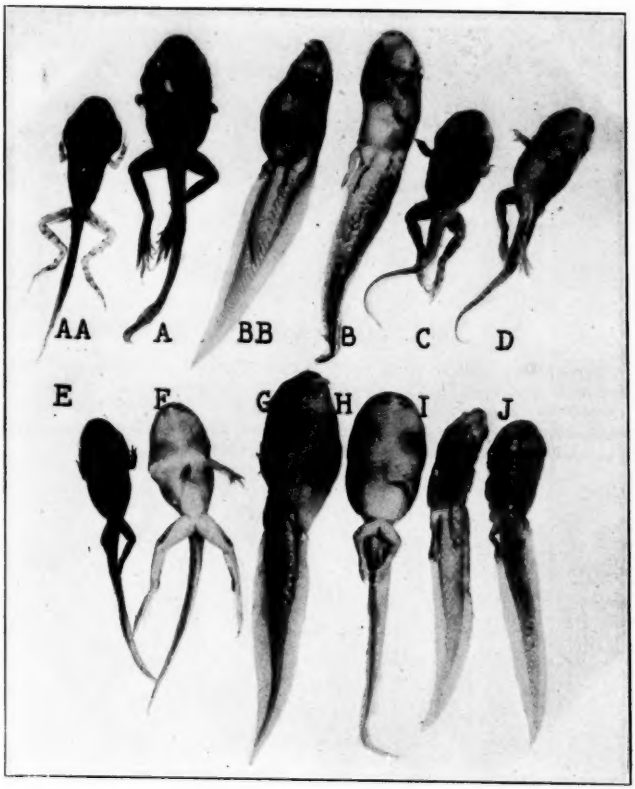
## PLATE IV.

Figures D to J. Normal Rana sylvatica natural size photographed in alcohol after fixation. The larvae (D to N) had reached their maximum size and were on the point of beginning a rapid metamorphosis when fixed. Note the shrinkage in size that has occurred during metamorphosis (B to J).


D
B
K
C
L
F
M
H
N
I
J

## PLATE V.

Figures A.A. to J. Thyreoidless Rana sylvatica, natural size. Photographed in alcohol after fixation. For size and number of doses of anterior pituitary substance administered see Table. Note G. which received no medication. The development is roughly proportional to the amount of pituitary given, and the size of the frogs is proportional to the size of the larvae before medication. A, C, and D died in the aquaria and became slightly swollen.


AA
A
BB
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C
D
E
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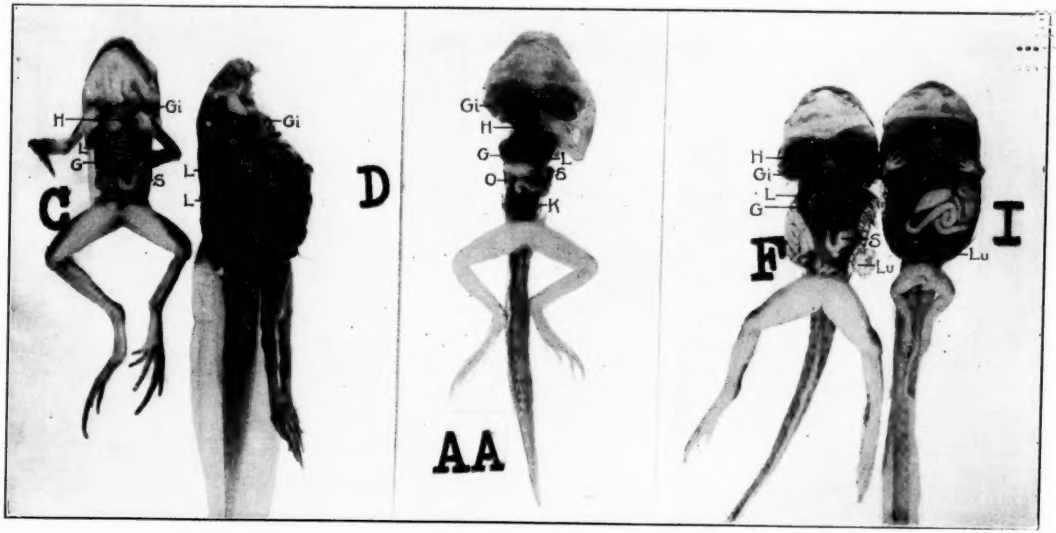
G
H
I
J

## PLATE VI.

Thyreoidless and control larvae and "frogs" of Rana sylvatica treated with anterior pituitary substance. Same animals as in Plate V. but dissected. X 3. C and D—Controls; AA, F and I—Thyreoidless.

Abbreviations: G.—Gall-bladder, Gi.—Gill, H.—Heart, K.—Kidney, L.—Liver, Lu.—Lung, O.—Ovary, S.—Stomach.


C
H
Gi
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AA
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S
Lu
Lu
I

TABLE SHOWING THE EFFECT OF TREATING THYREOIDLESS LARVAE WITH ANTERIOR PITUITARY PREPARATION.

| Beginning | 2 days | 4 days | 9 days | 10 days | 12 days | 15 days | 22 days | 31 days | Doses |
|---|---|---|---|---|---|---|---|---|---|
| mm. cc. | mm. cc. | mm. cc. | mm. cc. | mm. cc. | mm. cc. | mm. cc. | mm. cc. | mm. cc. | |
| A.A. 42-19.0-2.0-0.98 | 43.5-19.0- | 45-19.0-0.75 | 45-16.0- 5-0.65 | 45-14- 5.5-0.65 | 41-14- 6-0.75 | 42-14- 9-0.75 | 40-15-16-0.50 | 36.5-15-17-0.35 | *15 |
| A. 50-20.0-2.0-1.50 | 41.0-20.0-2.5-1.20 | 41-20.0-3-1.10 | | | 48-17-15-0.96 | 44-17-20-** | | | 18 |
| B. 46-20.0-1.5-1.30 | 47.0-20.5-2.5-1.10 | 48-19.0-3-1.00 | 47-16.0- 7-0.85 | ** | | | | | 8 |
| B.B. 47-20.0-2.5-1.20 | 48.0-20.0- | 45-18.5-3-0.80 | * | | | | | | 3 |
| C. 43-21.0-2.0-1.35 | 43.5-20.5-2.5-1.20 | 44-18.0-3-1.00 | | 44-16- 8.0-0.75 | | 40-15-13-** | | | 18 |
| D. 42-18.5-1.5-0.90 | | | 41-14.0- 5-0.60 | | 39-14-13-** | | | | 13 |
| E. 44-19.0-1.5-1.00 | | | 41-14.0- 5-0.55 | | 38-14-11- | | 36-14-12-0.40 | * | 21 |
| F. 45-19.0-2.0-0.93 | | 47-17.0-7-0.80 | | 45-16-13.-0.70 | | 42-17-18-0.56 | * | | 15 |
| G. 47-19.0-2.0-0.98 | | 48-21.0-2-1.06 | | 51-21- 2.0-1.08 | | 52-22- 3-1.40 | * | | 0*** |
| H. 53-23.0-2.5-1.45 | | 54-20.0-5-1.22 | 50-19.0-10-1.05 | ** | | | | | 9 |
| I. 46-20.0-2.0-1.05 | | 43-16.0-3-0.80 | 41-14.5- 7-0.50 | * | | | | | 9 |
| J. 44-19.0-2.0-1.00 | | 43-16.0-3-0.85 | 42-14.5- 7-0.65 | * | | | | | 9 |

N. B.—The first number, total length; the second, nose-anus length; the third, hind-leg length, all in mm.; and the fourth, volume, in cc.
*Killed. **Died. ***Control thyreoidless.

# PITUITRIN TEST

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In a previous article (1) the *adrenalin test* has been described. The subepidermal (s.e.) introduction of 0.05 c.c. of a 1:1000 solution of adrenalin (2) provokes the appearance of a swelling which, after a few seconds, or sometimes immediately, assumes a dark blue color, as if ink had been injected. Sometimes the periphery of the spot is red. The swelling then becomes surrounded by an alabaster-like halo, which grows in intensity and extent, often sending out irregular shoots in one or more directions. Around the white halo appears in turn another red halo, more or less intense in color and width. Frequently, a contraction of the pilomotor muscles of the skin occurs, which gives the appearance of goose-flesh to the alabaster zone.

The reaction in its complete form is therefore composed of the three following elements: 1. *Blue central spot,* 2. *White Halo,* 3. *Red Halo.* Having reached its utmost development in half an hour, after a stationary period, within an hour or so the reaction gradually disappears, the blue spot changing to red, leaving a slightly swollen red papule which in succeeding days goes through the usual stage of pigmentation.

By using a more dilute solution, for instance 1:200,000—1:1,000,000, the reaction is less intense, but nevertheless always manifest and preserves the same general type. It differs, however, by the absence of the central blue spot, generally substituted later on by a small red mark. This and the white halo around the alabaster swelling comprise in this case, the whole picture; the red halo is not always pronounced. The more dilute the solution, the later, up to 20 minutes and more, is the appearance of the response.

By further dilution the reaction becomes weaker, until it gets to be identical with the *indispensable* control reaction with distilled water. This water injection causes simply a white swell-

ing and a halo, which is not white but reddish. Briefly, the swelling becomes colored, afterwards to fade again with (always relatively) variable duration and intensity of the single phases in different subjects. A small reddish brown papule remains for one or more days and changes to a small brown spot (3).

The reactivity of the subepidermal adrenalin test in ordinary circumstances is usually included between dilutions of 1:200,000 and 1:000,000 (Parke, Davis vials). In some pathological conditions, however, it may be diminished or increased. We found it subnormal (viz., negative with these dilutions) in some cases of Addison's disease and of chronic adrenal insufficiency; increased (viz., positive with further dilutions, up to 5-20 millions), in some cases of disturbances of the menopause, of arterial hypertension, of Flajani-Basedow's disease and in some cases of pregnancy. Children give a weak reaction. Cases of profound anemia do not react.

Comparing in 26 cases the sensitivity to adrenalin administrated subcutaneously (s.c.) (1 cc. of 1 per thousand solution) and subepidermally (s.e.), we have had 21 cases of normal reaction in the s.e. test, no reaction to the s.c. test and likewise in two cases of s.e. hyper-reaction. In two cases of exaggerated s.e. reaction, there was only an increase of a few cm. of the arterial pressure to the s.c. test. Finally, in a case of scleroderma with arterial hypertension with normal s.e. test, the s.c. injection produced a marked reaction (notable increase of pressure, dizziness, tachycardia, tremor, traces of glycosuria). The failing cutaneous response may perhaps depend upon the sclerodermic lesion, although not macroscopically appreciable in the place of injection.

Another s.e. test, not hitherto described, is that with *pituitrin*. After what has been recorded the description of it is easy. Using the commercial solution, the reaction is identical with that obtained with a solution of adrenalin, about 1:200,000. Under ordinary conditions there is still a positive reaction with dilutions of about 1:500 of the commercial vials of pituitrin (Parke, Davis), but there is a delay in the appearance of the characteristic feature, the white halo about the swelling. We have found the reaction strengthened (positive even in dilution of 1:1000 and more) in arterial hypertension, in affections of the

pituitary body, in some cases of Flajani-Basedow's disease and reduced in some cases of chronic adrenal insufficiency.

Worthy of special mention is the circumstance that, if at times there may be a coincidence between the exaggerated or reduced reactivity to the two substances, in the great majority of cases *the pathological reactions to adrenalin and pituitrin are clearly shown dissociated and even opposed.*

We have pointed out that the solution of adrenalin at 1:200,000 gives approximately the same reaction as the vials of undiluted pituitrin; it has also been noticed that, although the reaction to adrenalin does not appear when the standard solution is diluted over five times (1:1,000,000), pituitrin, on the contrary, still maintains its special action when diluted to 500 volumes. The cause of this contrast is perhaps to be sought in the different points upon which the drugs exert their action, these being the neuromuscular junction in the one case and the muscle fibres themselves, in the other.

1. Ascoli (M.) and Fagiuoli (A.), Pharmacodynamic subepidermal tests, Accademia dei Lincei, 1919. After communication of this note we had occasion to read the review "The adrenin tests for thyroid disorders" in Endocrinology, Vol. II, No. 4. On page 463 the following passage appears: "This result was found to be remarkably constant. Not only does a 'hyperthyroid' patient react constitutionally to a subcutaneous dose, but also locally to an intradermic dose of one minim of 1-4000 solution of adrenin. This latter reaction depends upon the excessive contraction of the smooth muscle in the small vessels of the skin, supplied by the sympathetic, and is characterized by a central large area of blanching surrounded by a peripheral zone of reddening due to the neighboring secondary vasodilatation. In the blanched area a characteristic goose flesh is often seen. The reaction in a thyroid patient (exophthalmic goitre or toxic adenoma) lasts for 1½ to 2¼ hours as compared with ½ to ¾ hour in the normal subject. Whether the reaction will be found in other than thyroid cases has not yet been determined." We could not yet procure the original work of Goetsch, "Newer methods in the diagnosis of thyroid disorders: pathological and clinical. B. Adrenalin hypersensitiveness in clinical states of hyperthyroidism," N. Y. State Jour. Med., 1918, **18**, 259.
2. One stretches between two fingers laterally a small piece of skin of the anterior abdominal wall; where the skin is more distended, one introduces the point of a very fine needle attached to a small glass syringe, graduated in at least 1/20 cc. An essential condition is that the needle be pushed quite superficially under the epidermis, so that it is *clearly* visible underneath the skin: the injection must not be intradermal, but *subepidermal.* We insist on this point because the neglect of it may jeopardize the success of the result. One presses slowly the piston until 1/20 cc. of the desired solution is injected. As a measure of control in every experiment an injection of sterile distilled water at a distance of about 5 cm. must be made.

3. The practice of the simultaneous control injection of distilled water, as a test of the general reactivity of the skin *is never to be neglected.* Usually it presents the described type. At times, however, abnormal reactions are observed, which must be known. At times the swelling remains white for a long time (60-90 minutes); exceptionally the phenomenon of the goose flesh may appear. The quantity of liquid introduced and the depth of the injection are, moreover, important and must be considered. The involution time of the red papule, usually about 48 hours, is also variable. Unlike the s.e. injections of adrenalin 1:1000, and pituitrin undiluted, which cause almost no pain, dilutions with water are painful.

# A PLEA FOR SYSTEMATIC RESEARCH WORK IN THE ANATOMY, NORMAL AND MORBID, OF THE ENDOCRINE SYSTEM

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The above title may cause some reader to ask whether there really is anything wrong with regard to method in the present anatomical study of the endocrine organs. Indeed the great progress that our knowledge of the endocrine system has made during the last decades as well as the great profit that science has already reaped in this department are rather proofs of the contrary. Perfectly aware of this and of the importance that the methods of research so far used will doubtless have in the future as well, we must not shut our eyes to the fact that this study has its weak point, which forms a positive risk to the sound development of the new branch of science. This weak point is the want of a close anatomical insight into the organs in question.

First of all, I wish to show here that without such a deepened insight great departments of endocrinology must either remain completely inaccessible to us or at all events without sufficient stability.

It is a well known fact that *direct* lesions of endocrine organs occur, and frequently a certain clinical syndrome has more or less unanimously been considered to be connected with such lesions of one organ or another. To discern such direct lesions, at least when they are somewhat pronounced, our present knowledge has often proved sufficient. But, both in connection with exophthalmic goitre, Addison's disease, acromegaly and diabetes —to mention only some of the most studied ones—occur, as is well known, "formes frustes," in which the want of precision in our present anatomical knowledge is perceptible.

Another circumstance is, however, of still greater importance here. It is a commonly acknowledged and well-grounded experience that the endocrine organs are closely connected with each

other functionally, so that a disturbance in the function of one of these organs involves, according to the circumstances, a more or less profound disturbance in the function of a larger or smaller number of the others. Whether this state of things is characteristic only of the endocrine system or whether after more careful research anything of this sort will be also proved for other organs of the body, is another question, which it is not necessary to enter into here. It is sufficient here to establish that in such cases we must reckon not only with direct, but also with *indirect* disturbances of the endocrine organs.

But, indirect disturbances of the endocrine organs might not occur only in the cases in which the injurious factor ("noxe") has affected one or other member of the endocrine system. On the contrary, certain observations make it probable that in the case of other sorts of disease as well, the organs in question do not remain unimpaired. Thus, for instance, in the case of diphtheria and other infectious diseases, such an influence in many cases is established. It does not at present even seem absurd to presume that every disease of some duration and seriousness more or less affects the whole endocrine system, as is in fact, under such circumstances, always true of the thymus gland.

It may now be presumed that indirect changes of one kind or another, which up till now have for the most part not attracted any attention, are by no means always qualitative, perhaps not even chiefly so, but that there may also be, as in the case of the thymus gland, essentially quantitative changes. *But for the purpose of fixing quantitative changes with only a fair degree of certitude, our present knowledge of these organs is decidedly too limited.*

This circumstance may at least partly account for the fact that we have so little information about these indirect changes in the endocrine organs. Very often the system in question may even now be left without attention at the post-mortem examination and when really examined, no conclusions or only very vague ones are arrived at in the absence of an adequate acquaintance with the normal state of the respective organs. Which of us is able at the present time to tell how much or how little of the medulla of the adrenals is present in a man or woman at a certain age before the limits of the normal are exceeded?

What is our present knowledge of the extent to which the so-called gland of puberty is to be found at a certain age in a normal human sex gland? Or of the relation between the quantity of acinar and trabecular tissue in the normal thyroid? Or of the normal total number and size of the islets of Langerhans in the pancreas at a certain age? There is no end of questions of such a kind that crowd upon us in this sphere without our being able even to sketch an answer.

We may try to become acquainted with the real significance of the conditions outlined above: that at every disturbance of an endocrine organ, other endocrine organs too must be affected, that in other diseases these organs probably are also concerned without its being in our power to determine either the participant organs themselves or the degree to which they are afflicted. It really means that neither dissected material nor experimental work can, as matters now stand, by any means be made duly profitable to science.

As suggested above, in the first place normal data of comparison are a pressing need. Whether there is an increase or a diminution, whether too much or too little, can only be decided when we know sufficient about the range of the normal variation under corresponding circumstances as to age, sex, etc.

Our ignorance begins in connection with the mere size (the weight) of the organ. It is true that, even in the present literature, there is no lack of such *indications,* but I do not know a single one which, in the case of man, can even tolerably serve the purpose in question. They all suffer principally from two defects. First, in most cases mere averages are given. Nowadays, I suppose, no investigator holds the opinion that with regard to any organ averages can be given of such a nature that what does not agree with that standard should not be regarded as normal. Under such circumstances, averages are of comparatively little use. The important point is to determine as exactly as possible the normal range of variation. Mainly in order to give an orientation as to the position of an individual value within (or outside) the normal range the average may be of importance.

Secondly, the quality of the primary material hitherto published is mostly far from being sufficient for the present purpose. Generally, only the cases where obvious morbid alterations

of the organ in question were found or could be expected, have been excluded from consideration, while other cases of disease were considered available for statistical estimate of the normal organ. It is, however, quite evident that for the very purpose of creating a normal basis upon which eventual indirect organ lesions, affected by disease, can be recognized and evaluated, values thus acquired are quite useless. Only such organs as come from individuals who have suddenly died in full health and not by disease are available for the purpose. In the case of human beings, principally organs from murdered people, executions, accidents or suicides (1) will thus come into consideration for determining the normal range of variation. It may be unnecessary to point out that even in such cases the circumstances may give rise to criticism and exclusion of some cases. Anyhow, it does not seem necessary to enter into that question in this connection.

The mere determination of the limits within which the size of the organ—the weight of the organ—normally varies, is, however, only one condition for gaining available values in the following analysis of the organ. Generally, one will not make much progress by using merely the size of the organ. It is well known that a change in size may, under different circumstances, have quite a different bearing. A goitre represents sometimes an increase, sometimes a decrease, in the function of the thyroid. A reduction of the pancreas has a very different significance according to whether it has affected the exocrine or the endocrine component of the gland; an increase of the hypophysis or the adrenals, according as one or other of the heterogeneous components of the respective organ is affected, etc.

For this reason *we must elaborate for every endocrine organ special methods which admit of a quantitative—numerical—determination, with sufficient accuracy, of the material components of the organ.* In what manner such a method can be evolved for a particular organ can be gathered from a paper (Ztschr. f. angew. Anat. u. Konstitutionsforsch. Bd. 1.), where the writer set up the problem of fixing numerically the quantity of the cortex and the medulla of the thymus gland and the number and size of the Hassall's corpuscles.

Every organ has no doubt in this respect its own peculiar problems, a complete view of which can be obtained only by very

close attention to the subject. Some of these problems, however, are so obvious that they may be indicated without further investigations.

Thus, for instance, in the hypophysis, with accurate elimination of the connective tissue, the amount of each of the three principal portions ought to be ascertained. In the anterior portions the number of the different cell types, in the intermediate portion the number and size of the cysts with and without colloid should be approximately settled.

In the thyroid the weight of the true parenchyma similarly with deduction of the bulk of the connective tissue is to be ascertained; again, in the parenchyma the amounts of the trabecular and adenomatous territories, respectively, should be fixed apart from the acinar portion; and in the last mentioned part the number and size of acini with and without colloid should be calculated.

Similarly, in the parathyroid glands the true parenchyma, the trabecular and cystic tissue should be treated separately. Here, moreover, we meet with the task of approximating the relative and absolute numbers of the acidophil granulated cells.

With regard to the pancreas, the next object should be to ascertain the quantity of the endocrine and the exocrine parenchyma as well as to calculate the number and size of the islets of Langerhans.

In the adrenals the quantity of the cortex and the medulla as well as of the different zones of the cortex requires to be expressed numerically. Perhaps it will not prove quite impracticable with morphological methods to approximate the percentage of lipoids and adrenine in the organ, which would evidently be of the greatest consequence for estimating the state of function of an individual organ.

Concerning the sex glands, it is of special importance to ascertain the amount of endocrine tissue, in doing which for the ovaries, the corpora lutea and the other so-called lutein tissues should be considered separately. To settle the number and size of the ovarian follicles lies, as Valberg (1915) (2), has shown, within the bounds of possibility even in the case of a relatively large material. To figure the state of the spermatogenesis with fair accuracy seems, at all events in the case of a human being,

where the process passes on so irregularly, a difficult task; but it would, however, evidently be of great importance.

In all these enumerations we cannot stop at apparent or relative values; the real and absolute amount of every element of tissue treated must be approximately fixed. We must not forget that a relative increase of a structural element is perfectly compatible with an absolute reduction and vice versa, as I have stated in my above cited paper on thymus methods in general.

These hints may suffice to illustrate the type of problems which should, in the first place, be taken into account. It is not my object here to plan in detail the work on every organ with internal secretion.

That such problems can really be solved without insuperable obstacles is shown, inter alia, by a series of investigations on rabbits carried out from this point of view and dealing with most of the organs in question; these are recorded in another place (3). Similar investigations of the hypophysis and the adrenals in the albino rat have lately been published by Jackson (1917, 1919) (3a). Indeed, this author has even gone further in his analysis than I have suggested above, as he successfully treated both the frequency of mitoses and the size of parenchyma cells and nuclei.

Certainly, the cases mentioned here deal with the organs of animals and even of relatively small animals. Highly welcome as such researches are, not least as a basis for experimental work, the difficulties in procuring available material and analyzing the voluminous organs increase considerably, however, when the subject of the investigation is man. And it is precisely concerning man that we are in greatest need of the norms in question.

In the case, however, of at least one human organ of this kind, the thymus gland, I have found that investigations of this sort, even in the case of human beings, need not be considered impossible (4).

In the course of the last fifteen years, thanks to the liberality of several Swedish colleagues, I have been able to collect about 120 human thymus glands from post-natal life and about 60 specimens from intra-uterine life, which satisfy fairly well the demands made above. In analysing this normal thymus material, I have obtained norms for the different epochs of pre-natal and

post-natal life, against which can be tested values that have been gained with the same method in pathological cases. In this way it can be directly decided whether an organ from a case of disease shows any abnormality with regard to the absolute quantity of cortex or medulla, or to their reciprocal amounts, or with regard to the relative or absolute number of Hassall's corpuscles of one size or another. At present about 400 pathological cases have thus been analysed. The result as to certain categories of cases (exophthalmic goitre, "thymic death," certain acute infectious diseases, congenital lues) have already been published (5). The others are being prepared for publication. It seems to me as if certain of the results already gained are not only of an importance that is abundant compensation for the trouble taken, but also that they could scarcely have been obtained with the same degree of certainty by any non-numerical method.

I have now touched upon the second phase of the method of proceeding that I recommend here. It is evident that as soon as normal material, sufficient both in quantity and in quality, has been numerically analysed in the manner described, any case of disease, analysed in the same way, can with far more ease and, what is of still greater importance, with far greater certainty than at present, be estimated in all the respects that have been objects of the analysis. Just as in the case of the thymus, *by following the attained norms, we shall be able to decide whether a value from a case of disease falls within or outside the range of the normal and in what direction an eventual displacement has occurred.* It is a matter of course, that under these circumstances, too, the manner of proceeding can never be purely mechanical, but that the sane judgment of the investigator is always a decisive factor.

We shall also see how much here depends on the adequacy of the normal test material both from a qualitative and quantitative point of view. One single case, erroneously interpreted as normal, may be sufficient to give an undue extent to the normal range. And only as greater experience is obtained, are we able to conclude whether the range has been too limited in one set or other. It is also a matter of importance that, after all, for most of the organs in question a sex difference exists; we shall thus have to take into account both differences of sex and differences of age.

No doubt our claims as to the nature of the normal material will increase as our experience grows. Indeed, once the method of work that I plead for here prevails, this will come naturally.

It is, however, important that the method should, from the very beginning, be at once so exhaustive, so elaborate and with such careful foundations that it can claim to possess some stability or can even very soon become a standard for succeeding work. For, otherwise it is to be feared that with every improvement of the method that is found necessary, all the previous analytical work may be found inferior or defective and have to be done all over again. For this very reason I think methods that have been, as it were, improvised to answer the purposes of some special investigation do not come up to the mark. Every organ must be made the object of a comprehensive revision which takes into consideration not only the normal but also the morbid organ structure, the various functional changes, faults caused by shrinkage or swelling and otherwise during the technical treatment, etc. And before such a method is seriously put to practical use, its precision must have been duly tested. Furthermore, all this must be done for every separate species that is to be dealt with.

Here, indeed, an association of investigators for systematized co-operation, such as I have recommended in my paper upon constitution research work, would be of great use. *Would it not be rather a great thing for the Association for the Study of Internal Secretions to put upon its program the task of elaborating and standardizing such methods?*

In proportion as, by means of a numerical working-up of different morbid cases and their comparison with a normal test material, our knowledge increases, the obstacles to our going deep in this branch of science will disappear. In my opinion, there can be no doubt that this research work must be done sooner or later, and the sooner the better for science.

I am not disposed to try to prophesy what positive results will come from such a deepening of our present knowledge. Only, before I come to an end, I should like, more by way of example, to indicate some questions which will then be ready for exact treatment.

From different quarters the suggestion has proceeded that the mental diseases, or at least certain of them, are connected

with troubles in the endocrine system. Except for the experience that has been obtained with Abderhalden's method, results which can hardly be described as decisive, I do not know of any exact attempt to test this interesting hypothesis seriously. The method of working here recommended seems to pave the way for such a test.

The correlation between the brain and the endocrine system may also possibly be elucidated to some extent in that way. That such a correlation really exists is well known. In this connection it is enough to point to the splendid effect on the mental state that thyroid medication has had in certain cases of athyreoidism; or to remind the reader of the characteristic psychical habit in exophthalmic goitre, a habit which, after a successful reduction of the struma, may again give way to a normal state of mind, or to mention the changed mentality of the castrate, compared with the sexually normal individual. The instances could easily be multiplied. I think that the exact anatomical study of the endocrine system here opens the way to the biological aspect of mental activity, which should not be overlooked.

And a further point: only as far as we obtain an analogous exact knowledge of the organs with internal secretion in our experimental animals, can we lay a solid foundation for experiments designed to influence these organs therapeutically; and it is evident that this opens wide fields to us.

And, finally, by the kind of work recommended here an important preparatory step would be taken towards the realization of the still greater program of an anatomical constitution research, a subject to which I have tried to draw the attention of anatomists in the paper quoted several times above.

Indeed, each of the branches of work mentioned here alone is great and important enough to make the method of work recommended seem amply profitable. In order not to be misunderstood I might be allowed to make a further observation. I am far from thinking that the problems mentioned, or analogous ones, can be solved by this method *alone*. I would only emphasize that without a deepening of our anatomical knowledge by exact quantitative work we may never be able to solve them at all.

*A systematic numerical study of the anatomy of the endocrine system is thus a necessary condition for an exact treatment*

*of the important problems that are to be solved in this field.*

Upsala, September, 1919.

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# ADRENALIN IN ASTHMA. A CASE OF CHRONIC ADRENALISM

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The effect of the continued use of adrenalin has been so seldom reported that every well marked case demands the publication of its record. Accordingly we are submitting the following notes on a case occurring in the medical service at the Kansas City General Hospital.

## Case History

Female—Age 24—Married.

*Chief Complaint:* Asthma; Wheezing; Shortness of breath, paroxymal in type; Cough.

*History of Onset:* Six years ago the patient began to have coughing spells. These spells began in November and in the following January the wheezing began. The asthma has been practically continuous ever since. These attacks are the same throughout the year. They are always worse when lying down. At the time this trouble started the patient was pregnant and was working in onion beds. The patient has noticed that when she eats eggs, pears, peaches, and other fruits the attacks are made worse.

*Menstrual History:* She had had two children. Up until three years ago the menses were normal, but in the last three years she has had only two menstrual periods.

*History of Use of Drugs:* Since this trouble started six years ago the patient has been using adrenalin for the attacks, using about 7 c.c. daily. If deprived of the drug she became frantic. She also was addicted for a time to the use of chloroform inhalations. Up until a year ago she was also a user of morphine, the amount used not known. These habits were the results of attempts to relieve the almost constant dyspnea.

*Physical Examination:* Female appearing about 30 years of age, in good flesh (neither obese nor emaciated) walking about the ward. Her breathing can be heard for some feet away; she uses the accessory muscles of respiration.

*Head:* Scalp, ears and nose negative.

*Throat:* The tonsillar pillars are injected and covered by adhesions to the tonsils.

*Eyes:* The sclera is clear and both pupils are equal and react to light and accommodation.

*Neck:* Palpable glands at angles of jaws. Thyroid palpable.

*Chest:* Lungs—There is lack of expansion on both sides. The patient uses the accessory muscles of respiration. Tactile fremitus is decreased. The chest is hyperresonant. Both expiratory and inspiratory sounds are prolonged with various types of dry whistling rales throughout the respiratory cycle.

*Heart:* Cardiac dullness seemed normal. The heart tones are strong and regular and no murmurs are heard. Pulmonic second sound seems exaggerated. The blood pressure at the first examination was systolic 155, diastolic 140. At other times it was 160-98.

*Abdomen:* Because of voluntary rigidity of abdomen, the patient is hard to examine. There are no palpable masses of liver or spleen or notable tenderness.

*Skin:* Both arms and legs are scarred by the use of the hypodermic needle. On the forearms and ankles there are girdles of this scar tissue about four inches wide.

*Extremities:* Reflexes are normal.

*Death:* Patient died suddenly and unexpectedly. Her last dose of adrenalin had been 2½ hours before (1 cc.). Before death the patient was very nervous and noisy, throwing things about the room. She was found dead, lying on the floor, and when found appeared anemic. It had been discovered that patient had adrenalin and a hypodermic outfit and was self-administering the drug while in the hospital and for this reason she had been taken from the ward and put in a locked room.

*Previous Entrance to Hospital:* Entered Aug. 10, left Aug. 12, 1919. Entered Oct. 3, and left the same day, 1919. No record of findings on these entrances.

*Laboratory Findings:* Kidney function test, phenol-sulphonephthalein—15% excreted the first hour; 35% excreted the second hour.

*Blood Findings:* Red cells, 5,120,000; white cells, 8,400; hemoglobin (Tallquist) 80%.

*Differential Count:* Polymorph. neutrophiles, 53%; small lymphocytes, 27; large lymphocytes, 16; eosinophiles, 1; mast cells, 3.

*Cultures:* Cultures from sputum after giving KI gave growths of streptococci.

*Post-mortem Findings—*

*Chest:* The pleural cavity contained no free fluid. Both lungs were anthracotic. The left lung appeared normal. On cut section it showed areas of collapsed lung tissue intermingled with areas of compensatory emphysema.

The right lung was partially collapsed. There were adhesions from the lower border of the lower lobe posteriorly to the diaphragmatic pleura.

No obstructions along the respiratory tract were found. Cut section across the bronchi and their branches showed them to be patent.

The lumen contained some thick tenacious mucus.

*Heart:* The heart was slightly larger than normal. It was in systole, the left heart being firm and contracted. The right heart was dilated to a slight extent, with some hypertrophy of its musculature. The valves were normal. The coronary openings were patent and sclerotic. The aorta was normal in size, but contained several sclerotic plaques along the ascending portion and the arch.

*Abdomen:* No free fluid was found. The liver was enlarged and pushed downward and on cut section showed extensive fatty degeneration.

The stomach appeared normal. The spleen was twice the normal size and on section showed nothing abnormal. No pathological condition was found along the bile tract. The pancreas was normal. The intestinal tract was not otherwise abnormal but was very much congested. The appendix was normal. Both kidneys were congested and there were some drops of pus in the calyces of the right.

*Sexual organs:* Both ovaries were sclerotic, but the tubes appeared normal. The uterus was small and was in normal position.

*Vascular system:* All the large vessels were filled with fluid blood and no clots were found. There were small sclerotic patches along the aorta (round, not stellar).

### Reaction to Drugs

An attempt was made to ascertain the patient's reaction to the various antiasthmatics and glandular extracts. As will be seen from the accompanying charts, atropine and amylnitrite lowered the diastolic pressure, thus increasing the pulse pressure and affording some subjective relief. Pituitrin simply increased the blood pressure, and gave no relief. Corpus luteum (P. D. & Co.'s ampoule) gave no relief. Adrenalin gave varying results, of which two charts are given. Apparently the subjective relief was due to the increased pulse pressure.

The attempt to secure an autogenous vaccine failed, because of some slip at the laboratory.

The use of a nonspecific vaccine (typhoid, 50 millions) caused no reaction and no change in the subjective symptoms.

The patient was kept fairly quiet by exhibiting 15 minims of adrenalin per os every three or four hours. But this did not prevent her stealing chloroform or morphine whenever the opportunity presented. However, she did not secure enough of these to affect materially her condition; and the picture is one of the adrenalin habit—if it may be so called.

Whenever the patient was deprived of the adrenalin for a

half day, she would become frantic, and if allowed to go on would develop a cyanosis of lips and fingers, with a loss of the radial pulse—a condition so alarming that the attendants hastened to use the adrenalin and relieve her.

## DISCUSSION

Sajous states that "the prolonged use of adrenal preparations may induce chronic adrenalism, manifested by marked cardiac disorders, especially of the myocardium, dyspnea after slight exertion, tachycardia, high blood pressure, polyuria, icteric staining of the conjunctiva, and marked increase in weight." In our case, we noted cyanosis and circulatory failure on three or four occasions when we had attempted to stop the use of adrenalin, and to substitute other drugs. But at no time did we find evidence of myocardial disorders other than the decreased force, or pulse pressure. She was not obese.

Erlanger and Gasser believe as a result of animal experimentation that large doses of adrenalin do long-lasting damage to the circulation, if they do not actually carry the pressure down to a dangerously low level. "Peripheral constriction persists for hours." The heart develops irregularities under adrenalin. "The failure of the circulation is to be attributed to the extreme slowing of the blood throughout the body by the constricting action of the adrenalin on the arteries. It is concluded that the cause of the failure is the same as is operative after temporary partial obstruction of the vena cava or the aorta. This conclusion is justified by the fact that the most striking lesion found in animals dying as a result of any of these three procedures is alike in all cases, and consists of tremendous engorgement of the capillaries and venules of the villi of the intestines." Our findings would seem to be in accord with these experimental conclusions. For no lesion sufficient of itself to cause death was found. Even the collapsed lung would hardly do more than lower the vitality of the patient.

The small plaques found in the aorta show the beginning of the sclerosis, which we had expected to find in much greater measure.

It is interesting to note that the use of adrenalin even by the mouth gave some relief. The subcutaneous route also gave

systemic effects, so thoroughly was the patient sensitized to the drug. And as Cushny and other pharmacologists point out, the effect of the administration of the drug on the blood pressure varied from time to time.

Finally, we would call attention to the almost paradoxical effects on the blood pressure: namely, the increased peripheral resistance as shown in the diastolic pressure, and the weakened muscular power of the heart as shown in the decreased pulse pressure. This of course is in accordance with the statements of experimental pharmacologists.

SUMMARY

The history is recorded of a case of 6 years' duration in which the patient had taken approximately 7 cc. of adrenalin daily, for the most part with a hypodermic needle. She had occasionally used morphine and chloroform. Sudden death occurred. Aside from collapsed right lung and beginning aortic sclerosis, the chief post-mortem findings were congestion of the abdominal viscera, similar to that found in animals dead from adrenalin administration.

Addendum Note: Since the writing of the above, a case history of sudden death in an asthmatic has appeared (5). In this instance the patient was given frequent doses of adrenalin intravenously just before death, and the post-mortem examination showed the same congestion of the intestinal mucosa noted in our case. This congestion is probably the chief effect of the adrenalin.

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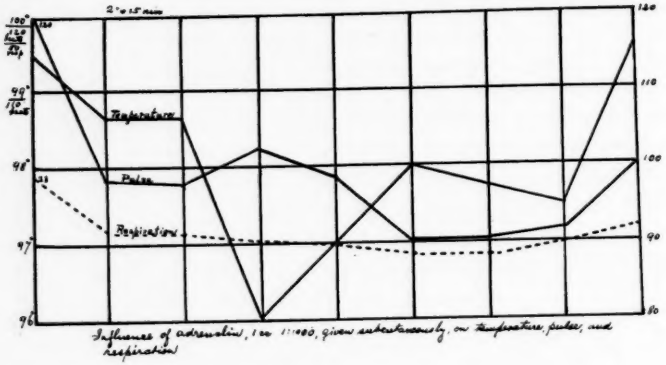
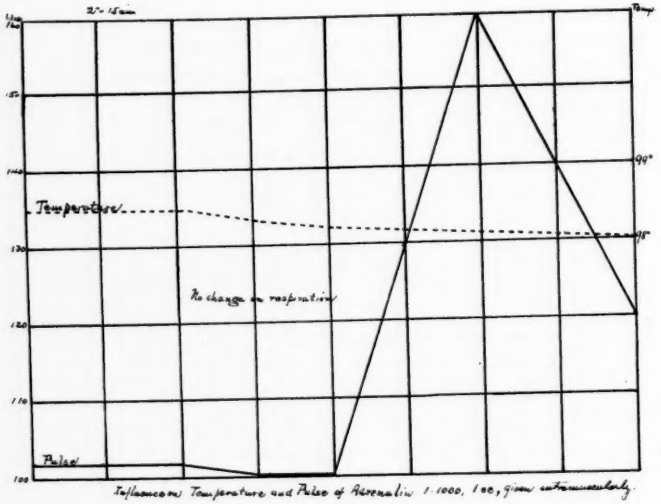
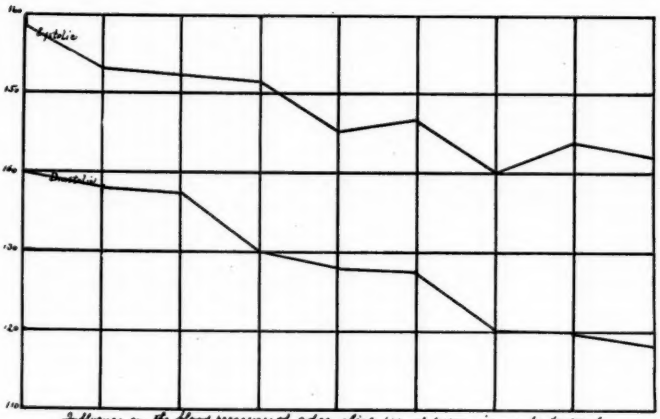
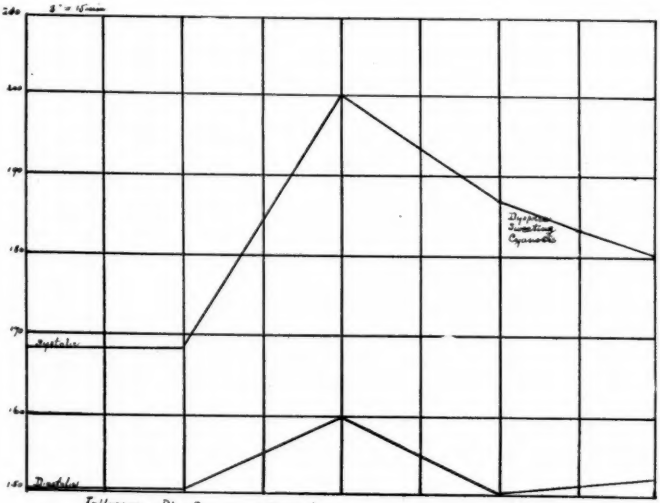

Temperature
Pulse
Respiration
Influence of adrenalin, 1 cc 1:1000, given subcutaneously, on temperature, pulse, and respiration

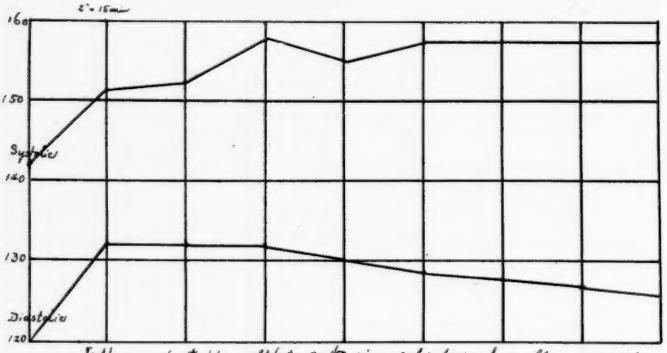

Temperature
No change in respiration
Pulse
Influence on Temperature and Pulse of Adrenalin 1:1000, 1 cc, given intramuscularly



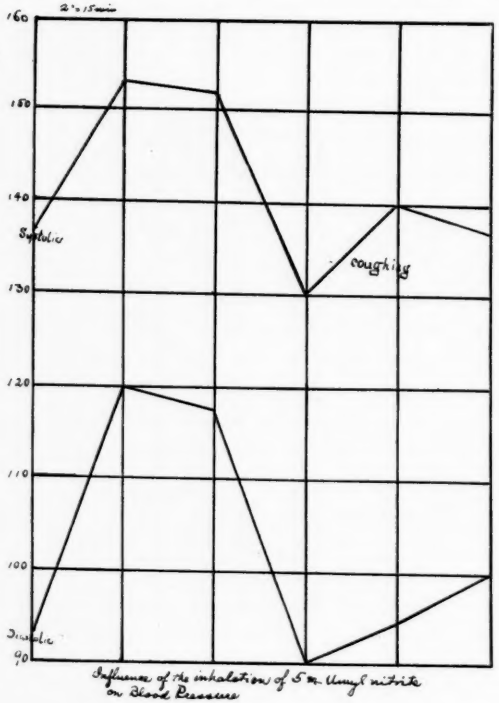

Influence on the blood pressure of adrenalin 1 cc of 1:1000, given subcutaneously.



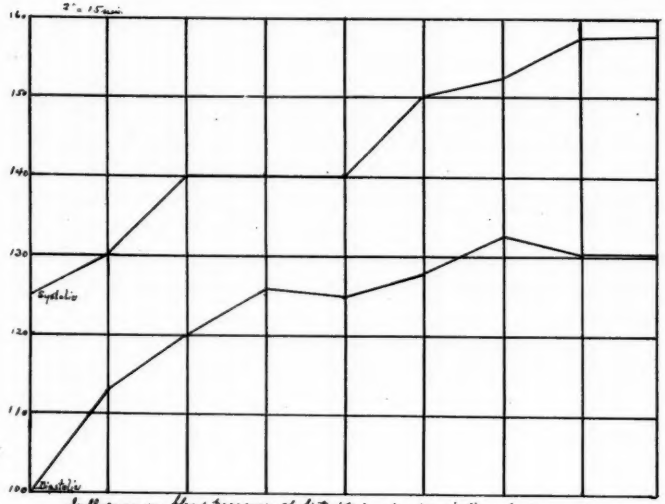

Influence on Blood Pressure of Adrenalin, 1:1000, 1 cc, intramuscularly.



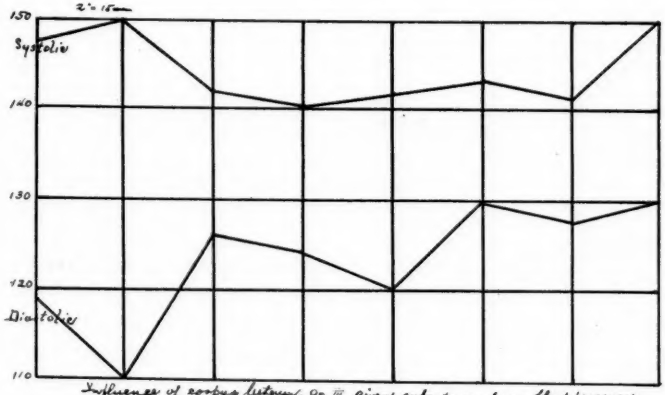

Influence of atropine sulphate, gr 1/50, given subcutaneously, on blood pressure.




Influence of the inhalation of 5 m. Amyl nitrite on Blood Pressure




Influence on blood pressure of pituitrin. 1 cc (surgical), subcutaneously.




Influence of corpus luteum, gr. iii, given subcutaneously, on blood pressure.

# THE INFLUENCE OF THYROID FEEDING UPON THE PHYSIOLOGICAL ACTION OF THE PANCREAS

By Hirotoshi Hoshimoto, M.D.

(From the Medical Clinic of Prof. K. Miura, Imperial University, Tokio.)

In the course of my experimental studies on the effect which thyroid feeding exerts upon the pancreas of white rats, certain interesting changes of the physiological actions were recently observed. I will attempt to describe them here very briefly; the full results of my investigation in the experimental hyperthyroidism will be described in detail and published subsequently.

Upon investigation into the biological activity of the pancreas, only the diastase is found to be contained in this gland in active form, while the other, i.e., proteolytic and lipolytic ferments, exist in an inactive state as trypsinogen and steapsinogen, and they must first be activated before they develop their own activity.

The test by Wohlgemuth's method shows the diastatic activity of the pancreas of normal, fully grown white rats fed on bread and milk for several weeks as follows:

D. 38° 30′=25,000-33,000 (the average 28,825) in nine normal male rats.

D. 38° 30′=16,700-50,000 (the average 26,620) in five normal non-pregnant female rats.

D. 38° 30′=24,717 the average of all rats of both sexes.

The amount of pancreas diastase per 100 mm. body-length was calculated to be:

D. 38° 30′=8,370-16,750 (the average 13,217) for male rats.

D. 38° 30′=7,800-18,560 (the average 12,511) for female rats.

D. 38° 30′=12,864, the average of all rats of both sexes.

During continuous feeding with adequate doses (0.5-0.1 gm.) of dry ox thyroid (containing 0.4 mg. of iodine per gm.) profound decrease of the diastatic activity of the pancreas occurred in the white rats of both sexes, giving the low value of:

D. 38° 30′=16,667, 13,900, 10,869, 9,240, 5,560, 1,262.

This result compared with the average value of normal rats, the decrease is estimated as 40, 50, 62, 67, 80, and 92 per cent.

My personal observations show that thyroid substance (extracted into physiological saline solution) does not at all check the amylolytic action of the diastase obtained from pancreas of rats; the diminution of the diastatic activity of pancreas should be ascribed to the actual diminution of the diastase contents of pancreas.

With regard to the relation of the decrease of diastase content to the morphogenetic change—diminution of acidophil granules—within the pancreas cells, which was found for the first time by M. Kojima in 1916, I confirm this result to coincide generally in the degree of diminution and its period of occurrence.

Administration of thyroid in relatively larger doses brought forth generally more profound decrease of pancreas diastase than that due to smaller doses.

But the individual difference in resistance against the toxic influence which thyroid substance exerts (disposition to hyperthyroidism) plays a more important role in this respect. Even in the same group of rats treated with similar doses of thyroid, some of them showed only slight decrease of diastase, while others showed marked decrease in relatively earlier stages of the experimental process.

The symptoms of thyroid intoxication are decrease of appetite, vanishment of liveliness, loss of body-weight, dyspnoea, and hypersalivation, the last of which should be regarded as a certain sign suggesting approaching death.

The decrease of diastase was not always accompanied by a poor appetite. On the first day of my experiment when the appetite was not yet affected and no emaciation visible, the diminution of diastase was already observed, and more so usually in the third week, in spite of good or rather abnormally augmented appetite. The decrease of diastase—for example that of 80 or 90 per cent—took place only in the rats which were suffering from extremely poor appetite, and showing other severe symptoms, such as dyspnoea, hypersalivation, etc.

The quantity of acid in the stomach does not agree with

that of diastase in the pancreas. The quantity of diastase in the intestinal juice obtained from the upper half of the intestines, i.e. from the duodenum and jejunum, was also estimated.

After the thyroid feeding the intestinal juice becomes milky, less yellowish, and more thick, showing a relatively lower value of diastatic activity, while in the case of fasting it appears very clear, deeply yellow, and less thick, giving comparatively higher value of diastatic activity. Even in normal rats it varies between:

D. 38° 30′=645 and D. 38° 30′=1,290, but has never gone lower than 645.

In some of the thyroid-fed rats the diastase of the intestinal juice was decreased to the low limit of normal rats, as also was the pancreas diastase, the former showing:

D. 38° 30′=320-133 and the latter 10,200-1,390, while in other cases it appeared as entirely normal or sometimes higher than normal, notwithstanding the decrease of pancreas diastase.

It must not be overlooked here that in such cases where intestinal juice contained normal or increased amount of diastase, appetite was never decreased, but rather augmented, and that such evidences were observed generally in the very early or in the later stages of continuous thyroid feeding and the diminution of the intestinal diastase was always accompanied by bad appetite and other severe signs.

Special attention was also given to the quality of the contents of the cecum and colon as well as to excreted feces. In the thyroid-fed rats the content of cecum was often very soft and yellowish white, showing many fat drops or crystals under the microscope, but none of the rats had suffered from diarrhoea. Excreted feces were always in natural form, even though they were sometimes quite soft, and in a few cases contained many fat drops, but such was the case only when the pancreas diastase was extremely diminished.

It has been found by M. Kojima that the pancreas of thyroid-fed rats after a certain duration of feeding becomes enlarged, and this was confirmed afterwards by P. T. Herring. I was also able to observe this in my experiments. The decrease of diastase contents was observed often in such enlarged

pancreases, when both the amount of food consumed and intestinal diastase were rather increased.

The diminution of pancreas diastase may be found sometimes also in emaciated rats, the general metabolism being shifted into pathological condition by certain exogenous or endogenous factors, exhausting or poisoning agents. Among my rats in reserve a female which after birth was giving its milk to eleven young, was very much emaciated and showed profound decrease of pancreas diastase. The same fact was observed in an emaciated male rat, its liver being occupied by more than twenty parasitic cysts.

Although a more or less marked loss of body weight, mostly owing to a rapid disappearance of fat, is well known as the constant results of thyroid feeding, I cannot explain the decrease of pancreas diastase as due simply to the disturbed general metabolism. The pancreas diastase begins to decrease even in the early days of thyroid feeding, although the general metabolism appears as entirely normal, there being no decrease of appetite, no loss of body weight, no vanishment of liveliness. The next fact contradictory to this explanation is that the diastase content of the intestinal juice is often of high value in spite of the diminution of pancreas diastase as already mentioned, while the decrease of pancreas diastase resulting from the decadence of the general metabolism accompanies generally a similar decrease of diastase in the intestinal juice.

The decrease of pancreas diastase in thyroid-fed rats cannot, therefore, be ascribed solely to the disturbance of general metabolism. At least in certain periods of thyroid feeding, when appetite is not affected, and intestinal juice contains much diastase, I should explain this as due to direct stimulation of thyroid autacoid upon the biological actions of pancreas, forcing it to discharge its ferments more quickly than in the normal condition.

P. T. Herring, describing the action of thyroid upon the general metabolism, has well compared it with a forced draft on the fuel in a furnace. My observation upon the pancreas has brought evident proof that thyroid acts in a similar way, as Herring stated, upon one of the digestive organs.

In connection with this description, a few words may be

added to explain the relation of diminution of pancreas diastase to the disappearance of glycogen in the liver of thyroid-fed rats. I have found that after 18 hours fasting almost 90 per cent of the glycogen disappeared in the liver of normal rats. Following decreased assimilation of carbohydrate in the alimentary canal, glycogen diminishes very rapidly in the liver. The disappearance of glycogen in the liver as the result of thyroid feeding, is observed in the rats which have poor appetite, consuming only a little bread and milk per day, but it is still evident in rats in the later stage of thyroid feeding, when the appetite is regained or rather augmented, i.e., the amount of food consumed is more than doubled and the pancreas is already enlarged, containing greater quantity of diastase than in normal rats, while the diastatic activity of intestinal juice is normal. It seems evident that the diminution of pancreas diastase takes only a small part, or sometimes no part, in decreasing the glycogen in the liver. This can be ascribed to the direct influence of thyroid upon the liver (or upon its nerves) or to the increased general metabolism, stimulated by the excess of thyroid autacoid.

Certain clinical observers such as W. Falta, A. Schmidt, Salomon and Amalgia, Schüler, and A. Bittorf noticed steatorrhoea in several cases of Graves' disease. How this symptom develops there is no decided opinion, but most of the observers agree. Falta ascribed it to insufficiency of the internal secretion of pancreas produced by the influence of thyroid, while Bittorf asserts that the insufficiency of the external secretion of pancreas causes such a symptom. The discussion on this problem is based upon clinical observations upon the effect of pancreon administration or on the quality of feces.

Toulay has estimated the diastase in the urine in case of Graves' disease, but failed to confirm the decreased activity of the external secretion of the pancreas.

No investigator has successfully studied the biological actions of pancreas itself to explain this phenomenon. The question whether this may be caused by the deficiency of external secretion or due to disturbance of the internal secretion of the pancreas is yet to be decided.

Another important point among the investigators exists in the question whether the lesion of the pancreas itself is due to the excess of the thyroid influence (hyperthyroidism) or to the agent which produces chronic lesion in the thyroid gland.

During my experiments I have observed under the microscope many fat drops and crystals (stained by Sudan III) in the feces excreted by some of the thyroid-fed rats, the pancreas diastase being extremely decreased, while in the feces of normal rats when fed on bread and milk, not any fat drops were observed (these having been of course previously fed on a similar diet).

From these observations I can assert without hesitation that steatorrhoea may be caused by hyperthyroidism (excess of the thyroid autacoid in the body), and the deficiency of the external secretion of the pancreas plays an important role herein.

## SUMMARY

Nine normal male and five normal, non-pregnant female white rats were fed for several weeks on bread and milk. The diastase content of the pancreas varied (Wohlgemuth's method) from 25,000 to 35,000 units in males and 16,700 to 50,000 in females. The average for both sexes was 24,717. Feeding dry thyroid in dosage of 0.5 to 0.1 gm. resulted in a marked decrease of the diastatic activity of the pancreas varying from 40 to 92 per cent. This was accompanied by a diminution of the acidophile granules of the pancreas cells. Large doses of thyroid were more effective than small, but the effects in different animals were variable. The diastase content of the intestinal juice was also decreased in some cases by the thyroid. In such positive cases the appetite was markedly depressed and the feces were soft; in extreme cases they contained considerable quantities of fat. Thyroid feeding frequently resulted also in marked enlargement of the pancreas. In such cases the pancreatic diastase was often decreased even when the amount of food consumed and the intestinal diastase were augmented. The decrease can not be ascribed to general metabolic perturbation since it frequently antedated any evidence of such. It is rather ascribed to stimulation of diastase discharge from the pancreas.

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# THYROID DIABETES

G. L. Rohdenburg, M. D.

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The relation of the thyroid to carbohydrate metabolism has often been commented upon, von Noorden having described, many years ago, what he termed thyroid diabetes. The more recent investigations initiated by Jacobsen (1), and more fully developed by others (2), have emphasized this relation still further. As is well known the work of Jacobsen and others has shown that the ingestion of considerable amounts of glucose is followed by a temporary hyperglycemia. It is generally accepted that when, in the course of this hyperglycemia, the concentration of the blood sugar rises above 185 mgm. per 100 c.c. of blood, in the majority of cases sugar appears in the urine. McCasky (3), who investigated this phase of metabolism in some thirty odd cases of exophthalmic goitre, was unable to demonstrate a specific curve of sugar tolerance in the blood during the disease, although, in common with others, he noted that there was a hyperglycemia even before the administration of glucose. Janney and Isaacson (4), found that the complete extirpation of the thyroid, in dogs, was followed by absence of hyperglycemia when large amounts of glucose were administered.

Theories attempting to explain the mechanism of sugar mobilization based on the data at present available are all unsafe, since no theory as yet advanced is sound enough to withstand the application of facts already demonstrated but disregarded in the formulation of any given theory. It may perhaps be permissible to state here that the question of glycemia and the glycemic reaction which follows either the ingestion of large amounts of glucose or the subcutaneous injection of a variety of organic and inorganic substances has a twofold significance: one directly concerned with metabolism, the other associated with the processes of immunity. These phases are considered in other publications (5).

The cases reported in the present article are of interest in that they apparently substantiate the current theory of the influence of the thyroid upon sugar metabolism, and for the suggestion they offer as to the possible etiology of the condition.

*Case 1.* While the following cases have been grouped as one, in reality four individuals were concerned. Two sisters with uneventful past and family histories developed what clinically appeared to be diabetes, one at the age of 45, the other at the age of 49. Both of these age periods corresponded with the actual cessation of menstruation in the respective individuals. The sister, Mrs. B., married a man who, at the age of fifty-six, developed diabetes. This couple had two sons. The first son was nondiabetic, and died at the age of twenty-three of a brain abscess following a mastoid infection. The second son developed diabetes at the age of eighteen years, and has been under observation for a period of seven years.

In order to present more concisely the salient facts in this interesting family, it may be stated that all examinations were negative, except for the positive facts that all the individuals were large and exceptionally well nourished, and that in each case the presence of sugar in the urine was associated with polyuria, at times itching of the skin, and excessive thirst. All four patients had been under observation for a period of about fourteen months, and had been placed on various restricted diets [the Allen treatment had not at that time (1909) been proposed], and had received various types of medication, i.e., codeine, atropine, etc. All of this was without appreciable effect, the urinary sugar varying between 2 and 4 per cent under restricted diet. For a period of approximately two years, several of the endocrine glands were administered per os. The changes in the urinary output of sugar under the influence of this type of medication were at times uncomfortably startling.

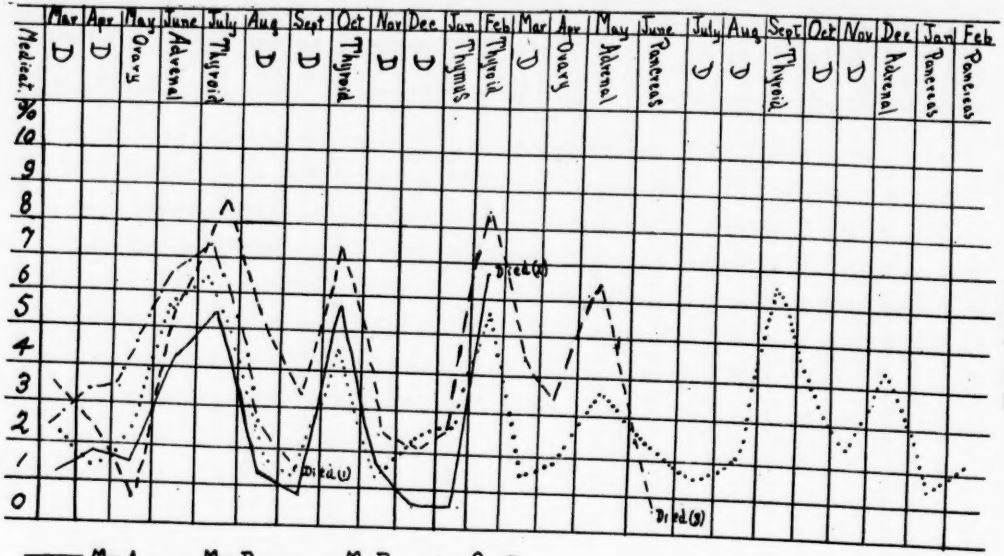
Chart 1 presents in graphic form the variations in percentages of urinary sugar under different regimes for all four cases. During this entire period the family were under dietary restrictions of a general type, but during the months indicated by "D" the restrictions were severe, the patients receiving only fat, proteins, and the broad group of vegetables growing above the

ground—peas, beans, and lentils excepted. During the months marked with one or another of the gland extracts, the desiccated gland was given in the dosage of three grains, three times a day. Urinary examinations were made weekly on twenty-four-hour specimens by the Fehling method, and the figures presented in the chart are the averages of the four examinations per month. The chart speaks for itself in that it shows in a striking manner the increased output of sugar when desiccated adrenal or thyroid gland was given, and the return to lower values when this medication was discontinued.

Interesting as these observations are, the subsequent course of events in each case is still more interesting. Mr. B. died in in a typical diabetic coma; autopsy was not obtained. Mrs. B., after some financial reverses, committed suicide by using illuminating gas. Mrs. A. died of sepsis following a typical diabetic carbuncle of the neck. Son B. passed from my observation temporarily some six months after the last month indicated on the chart. I saw him again five years later (1915), when he gave me the following history. About six months after seeing me for the last time, he had developed rapid heart action and considerable exophthalmos, and after four months in bed with no improvement, a portion of his thyroid was removed. This statement as to removal of the thyroid was borne out by physical examination. He had occasion to have his urine examined about six months after the operation and it was found to be sugar-free. The consumption of two pounds of grapes (Malaga) and three ice cream sodas within twelve hours at the time of his visit failed to produce sugar in the urine.

We have, then, in this family group a history of diabetes in one of the ancestors, the development of diabetes in two sisters at the time of the menopause, and the development of diabetes in one son at the time of puberty. We know that at these periods the thyroid is profoundly affected by the general changes in the organism. Again, the administration of thyroid gland repeatedly caused a marked increase in the sugar excretion; and, finally, the removal of part of the thyroid gland in one member of the family was followed by the disappearance of glycosuria.

*Case 2.* The second case is the reverse of the previously cited Son B., in that the development of Graves' disease oc-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Mrs A - - - Mrs B —·—·— Mr B ····· Son B.

Chart 1

D = diet restricted. Sugar % based on average of 4 determinations made each month.

(1)- Diabetic Coma (2) Sepsis, Carbuncle

(3)- Suicide.

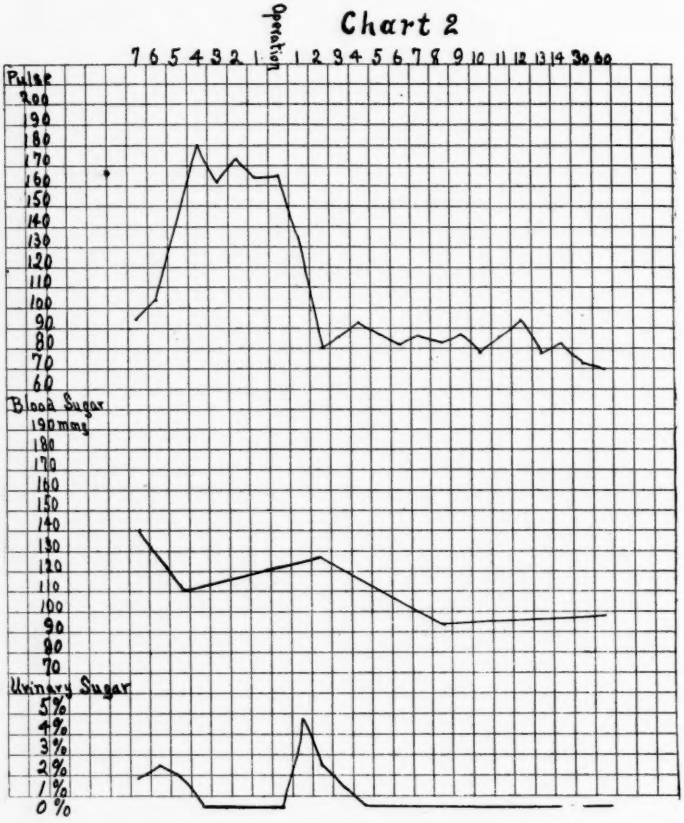
curred first and the development of diabetes second, and finally, a cure of both conditions followed removal of a large portion of the thyroid gland. In this case also we have more exact chemical details.

An American woman, married, aged fifty-three years, and a nullipara, gave the following history. Her family history was negative except that her father had died of diabetes. The other members of the family were of large frame and exceptionally well filled out, though she was small and would not be considered even plump. Her past life had been unusually strenuous, with many excessive demands upon both her physical and her mental energy. Her past history was without interest, except that in 1915 she had suffered from symptoms of excessive thyroid activity, with rapid pulse, loss of weight, and a typical tremor. Because of this condition one lobe of the thyroid was removed under local anesthesia by Dr. George H. Semken, to whom I am indebted for the case. The operation was followed by great improvement in her general condition, her weight increasing by fifteen pounds, and her pulse falling to 100. She was very definite in stating that for a number of years previous to her operation she had had a pulse ranging from 120 to 140.

Her present complaint was that during the past year she had noted a loss of thirty-five pounds in weight, polyuria, excessive thirst, and some itching of the skin. About six months ago she was told that she had diabetes; the percentage of sugar found was not stated. Physical examination at this time showed as the only abnormalities a systolic murmur at the base of the heart with roentgenographic evidence of a dilated aorta; pulse, 90 to 100; blood pressure, 95 d., 140 s.; and a subserous fibroid about the size of a lemon. No exophthalmos was noted. The Wassermann reaction was negative, and the blood count normal. The urine for four days on a full diet showed from 1.8 to 2.5 per cent sugar without evidence of acidosis; the blood sugar value was 140 mgm. per 100 c.c. The curve of sugar excretion and of pulse rate are shown in Chart 2.

A clinical diagnosis of diabetes having been made, the patient was starved. The urine voided after sixteen hours' starvation was sugar-free, but showed acetone and diacetic acid. After twenty-four hours' starvation the patient commenced to vomit,

and within a few hours was vomiting every three to ten minutes, bringing up mucus and bile. At the same time her pulse rose rapidly to 180 at the wrist (as nearly as could be determined). She was given a Murphy drip with a teaspoonful of sodium bi-




carbonate to the quart, in spite of the fact that the $CO_2$ combining power of the blood plasma was 55 volumes per 100 and sugar-free, broth was given per os. After twenty-four hours the vomiting ceased, the pulse remaining as rapid as before.

After five days of rapid pulse (160-180), the urine remaining sugar-free, Dr. Semken extirpated the other lobe of the thyroid under local anesthesia, leaving the isthmus in situ, the diagnosis of hyperthyroidism being evident. The day after the operation the urine showed 4.8 per cent of sugar; the next day, 2.4 per cent; the third day, 0.5 per cent, and on the fourth day was sugar-free. This sudden increase in urinary sugar was undoubtedly due to the sudden expression of thyroid secretion into the blood current due to operative manipulation. The pulse fell rapidly until, two days after the operation, it was 80 per minute. One month after the operation the patient had gained twenty-five pounds; her pulse was 72; and the ingestion of two ounces of cane sugar in twenty-four hours plus a diet consisting wholly of carbohydrates for two days previous and for the day of the test failed to produce any renal leakage of sugar. Three months after the operation she had gained an additional ten pounds, the pulse was 70, and on an unrestricted diet the urine was sugar-free.

The cases described above suggest some interesting trends of thought. The etiology of diabetes is most obscure. The disease may be induced in a variety of ways, ranging from injury to the nervous system, as shown by the classical piqure experiment of Claude Bernard, to extirpation of the pancreas or poisoning by phlorhizin. Still, even though extirpation of the pancreas does give rise to diabetes, it is the experience of every pathologist that carcinoma of the pancreas may destroy practically the entire organ and not give rise to glycosuria. The experiments of Janney and Isaacson, previously referred to, and the experiences in the cases cited here suggest that it may after all be possible that the condition is a manifestation of thyroid overactivity and not primarily of pancreas insufficiency, as is now commonly accepted. Personally, until the occasion of Case 2, we had lacked the courage to repeat thyroid feeding in cases of diabetes; but we now feel inclined, should the opportunity again present itself, to try the feeding of this gland; in the event of an increase in urinary sugar, after such feeding, a partial thyroidectomy could be rationally advocated.

SUMMARY

The author cites a family in which glycosuria was increased in intensity after the oral administration of either thyroid gland or adrenal. One member of this family was cured of his glycosuria after a partial thyroidectomy. In a second case the patient has previously had a portion of the thyroid removed for exophthalmic goitre, developing glycosuria several years later. The glycosuria in this case also disappeared after extirpation of more of the thyroid gland.

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# THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE (1917 CASES) WITH A BRIEF DESCRIPTION OF THE TECHNIC USED AT THE MAYO CLINIC

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"In each mammal there is a basal metabolism" (19). By the term "basal metabolism" or better, "basal metabolic rate," of an organism is meant the minimal heat production of that organism, measured from twelve to eighteen hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined directly by actual measurement by means of a calorimeter, or indirectly, by calculating the heat production from an analysis of the end products which result from oxidation within the organism, or specifically, from the amount of oxygen used and the corresponding amount of carbon dioxid produced, together with the total nitrogen eliminated in the urine (although, for clinical work the urinary nitrogen may be neglected).

The experimental work of Lavoisier (17) marks the beginning of researches on metabolism, and to him belongs the conception that the life processes are those of oxidation with the elimination of heat. Technically, the problem was beset with many difficulties, for it was necessary not only to measure the amount of heat lost by radiation and conduction from the body (direct calorimetry), but also to collect accurately the various end products resulting from combustion within the body, from which data the heat production can be calculated (indirect calorimetry), in order to prove from a comparison of the results obtained from the two methods that the law of conservation of energy also holds for the living organism. Furthermore, before the method of indirect calorimetry could be employed the heat values of carbohydrate, fat, and protein had also to be determined in order to calculate the heat derived from their combustion in the body. The solution of these problems was greatly advanced by Carl Voit (23) and his pupils, the chief of whom

were Pettenkofer (22) and Rubner (27). The heat values of carbohydrate and fat were readily determined by Rubner (25) since these two substances are oxidized to the same end products (carbon dioxid and water) whether burning in the body or in a calorimeter. In the case of protein, however, the problem was somewhat more difficult, for a part of the end products of protein combustion in the body is eliminated in the urine and feces and the latent heat thereby lost had to be subtracted from the heat value of protein as determined in the calorimeter.

In 1894 Rubner (26) constructed the first successful respiration calorimeter designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it and the simultaneous measurement of the quantity of heat produced by that organism. By means of this apparatus Rubner verified the method of Pettenkofer and Voit of calculating the heat production (indirect calorimetry) and he proved that the law of conservation of energy holds for the living organism.

It was not until 1905 that the respiration calorimeter was brought to a high degree of technical perfection by Atwater and Benedict (1). With their apparatus it was possible to determine simultaneously with the measurement of the heat elimination, not only the carbon dioxid production, but also the oxygen consumption of the subject. Studies made by Benedict and his associates, at the Carnegie Nutrition Laboratory, using the perfected calorimeter, have added greatly to the exactness of our knowledge with regard to the metabolism in prolonged fasting (4), the metabolism of normal persons (6), of infants (8), and of diabetics (7). They also confirmed the agreement between direct and indirect calorimetry. Lusk (18) and Du Bois and their co-workers have likewise demonstrated, in a large series of pathologic conditions, the close agreement between the two methods. As a result of these investigations the use of such a complicated apparatus as the respiration calorimeter has been shown to be unnecessary for clinical work and that in its place the comparatively simple method of indirect calorimetry may be used.

Krogh (16) of Copenhagen, and Carpenter (11) of the Carnegie Nutrition Laboratory, have described and compared in

great detail the various kinds of respiration apparatus used in indirect calorimetry. Carpenter has shown that for indirect determinations two types of apparatus are suitable, the closed circuit and the gasometer.

By far the best apparatus of the closed circuit type is the Benedict unit apparatus (2). By means of a mask, mouthpiece or nasal tubes, the subject rebreathes air from a closed system in which the carbon dioxid is absorbed by soda lime, and, as the oxygen is used up, it is replaced by oxygen in known amounts. The air within the apparatus is kept in constant circulation by means of a blower. A small spirometer is inserted in the circuit as an expansion chamber and volumetrically records the respiratory movements on a smoked drum. Knowing the weights of oxygen used and the carbon dioxid eliminated, one can readily calculate the heat production. As pointed out by Carpenter, this apparatus is very satisfactory and indeed the best for many purposes, especially when used in conjunction with a calorimeter or with the cot-chamber calorimeter described by Benedict and Tompkins (9). We have found, however, that for clinical work the unit apparatus is rather cumbersome. It requires constant checking to see that it is absolutely air tight, for a leak of 20 or 30 c.c. during a fifteen minute determination will appreciably affect the result, because such a leak in this type of apparatus will be equivalent to the loss of so much oxygen and not equivalent to the loss of so much air as is the case in the gasometer method. Furthermore, the accumulation errors of the apparatus fall on the oxygen and not on the carbon dioxid determination, thus causing an error in the calculation of the respiratory quotient and heat production. The absorbing chemicals must be changed frequently and with the repairing and constant checking of the apparatus it is on the whole difficult to use in clinical work, particularly if many determinations are to be made.

The portable respiration apparatus recently devised by Benedict (5) for clinical work is a modification of his unit apparatus described above. It is designed primarily to give a rapid and at the same time a comparatively accurate measurement of the oxygen consumption without involving analyses or weighing. We have not adopted it, as we prefer to determine not only the

oxygen consumption, but also the carbon dioxid elimination since the heat production can thereby be more accurately calculated. Moreover, the difficulties inherent in the closed circuit type of apparatus are still present in the portable apparatus.

For clinical work the gasometer method introduced by Tissot (29) in 1904 is considered by us the most satisfactory. Briefly, the determinations are made in the following manner: A mask is adjusted over the patient's mouth and nose and by means of expiratory and inspiratory valves the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of the carbon dioxid and oxygen content of the expired air, the analyses being done in the Haldane gas analysis apparatus (14). Since the ventilation rate for each minute is known, as well as the amount of carbon dioxid produced and the oxygen absorbed, it is possible to calculate by means of calorie tables the total number of calories produced each hour.

The following points in the routine determination of the basal metabolic rate deserve further discussion: To obtain comparable results the patient must be in the postabsorptive condition, that is, he must fast for at least twelve hours preceding the test. It is very important that this rule should be observed, because all kinds of foods cause an increase in the heat production and this effect may not entirely disappear for twelve hours after their ingestion (28). Moreover, the patient must be at complete rest and the effects of previous muscular exertion eliminated by requiring him to rest in bed for twenty minutes before the test is started, for we have shown in a series of experiments that a rest period of this length of time is quite sufficient to obtain the basal metabolism (10). During the preliminary rest period an observer sits with the patient, noting at intervals the character and rate of the heart beat and the respiration; likewise, about the middle of the period, the blood pressures, both systolic and diastolic, are obtained. After twenty minutes' rest a mask is accurately adjusted over the nose and mouth of the patient and securely held in place by means of tapes so that there is no leakage of air around the mask (Fig. 1). A mask is preferable to either a mouthpiece or nasal tubes. With a little experience it is possible to adjust the mask

so that it is not only comfortable for the patient, but also air-tight. One of the chief advantages of the gasometer method is that should a very slight leak of a few cubic centimeters occur around the mask during the course of an experiment the end

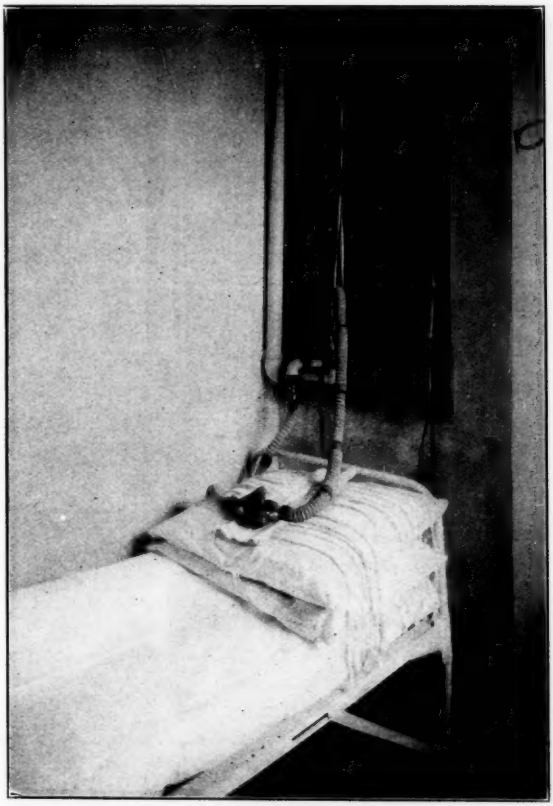

Fig. 1. Mask and connections showing valves, intake pipe and towel with tapes.

result is not appreciably affected, while a leak of a similar volume in the closed circuit apparatus has a value at least five times as great, because in the latter case it is equivalent to the loss or gain of so much pure oxygen.

During the test proper the observer sits with the patient, recording his pulse and respiration rates and noting and recording on a special chart any movements. Care is taken to impress on the patients that even slight movements materially affect the

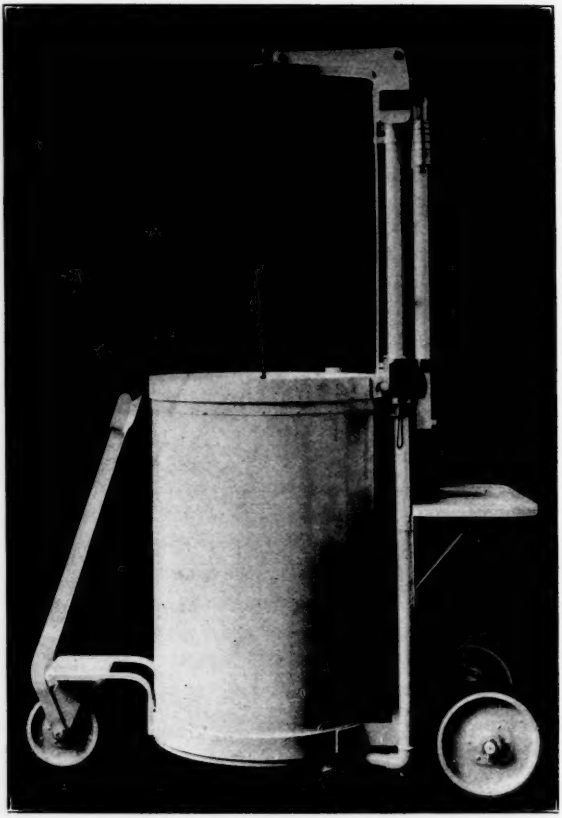

Fig. 2. Moveable gasometer.

test and it is almost always possible to obtain their complete co-operation. Sometimes, however, in an extremely nervous person, a basal rate cannot be obtained on the first test. Instead of repeating the determination the same day the patient is in-

structed to return the following morning for a second test. In such instances the rate will occasionally be ten points lower than that obtained the first time when the patient was unduly nervous and frightened about an unknown procedure.

The total volume of the expired air is collected in a gasometer (Fig. 2) over a known length of time. Unlike in the work with the closed circuit apparatus no appreciable error is introduced by failing either to start or stop the experimental period at exactly the end of a normal respiration, a difficult thing to do with accuracy in the case of patients who breathe irregularly. Samples of the expired air are then collected over mercury in sampling tubes and analyzed in duplicate for carbon dioxid and oxygen. Approximately 10 c.c. of expired air are transferred into the burette of the Haldane gas analysis apparatus (Fig. 3) and after adjusting certain levels the reading of the initial volume of the sample is made, reading to the nearest 0.001 c.c. The gas sample is then passed back and forth over a solution of dilute potash to absorb the carbon dioxid. The levels of the solution are again adjusted and a second reading of the volume of the remaining gas in the burette made. The contraction in volume of the gas, due to the absorption of the carbon dioxid by the potash solution, divided by the original volume, gives the percentage of carbon dioxid in the expired air. In like manner the percentage of oxygen is determined, potassium pyrogallate solution being used as the absorbent for oxygen.

The gasometer method is particularly suitable for clinical work because each step in the procedure can be checked by a second assistant, reducing to a minimum the chance of technical errors. Although the method requires care and accuracy in every part of the procedure, it is possible to teach the technic to laboratory workers who have had no preliminary scientific training other than that obtained in a high school. The most difficult step in the procedure is the analysis of the expired air. This, however, we have found to be inconsiderable. Our assistants can obtain routinely duplicate analyses agreeing within 0.04 per cent for carbon dioxid and 0.06 per cent for oxygen, and they are able also to take entire care of their gas analysis apparatus. The equipment necessary for this method is simple and inexpensive and when properly constructed

is rarely out of order and, except for cleaning, requires very little mechanical care. Furthermore, the apparatus is free from the many mechanical difficulties inevitably inherent in a closed circuit system in which the air current is driven by an electric

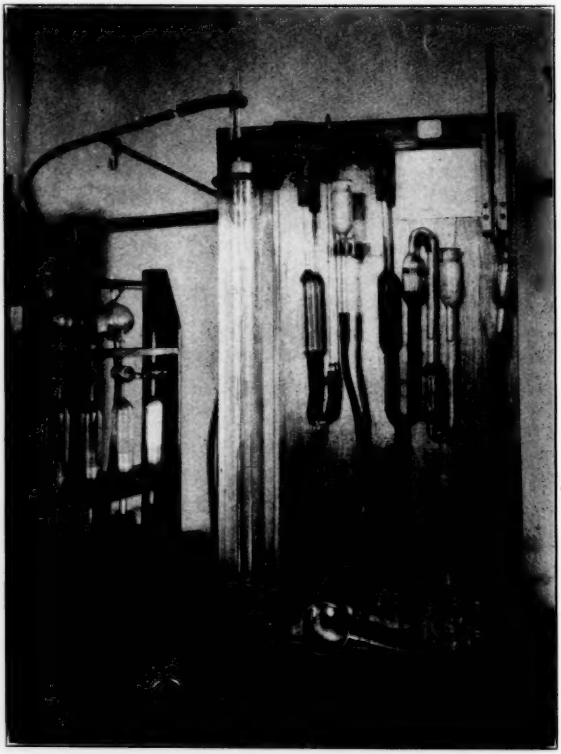

Fig. 3. Haldane gas analysis apparatus.

pump. In the metabolism laboratory at the Mayo Clinic we are averaging 30 cases a day and have developed a very definite and routine procedure which has decreased the chance of technical error to less than 1 per cent.*

* The details of the technic are described in a laboratory manual by Boothby and Sandiford (10). The apparatus may be obtained from H. N. Elmer, 1136 Monadnock Bldg., Chicago.

The calculation of the basal metabolic rate from the experimental data is very simple. Knowing the volume of air expired by the patient in a minute (the ventilation rate) and the percentage of carbon dioxid and oxygen in the expired air, it is possible to calculate the volume of oxygen absorbed by the patient in one hour, as well as the corresponding amount of carbon dioxid produced. Since the respiratory quotient, that is the ratio between the volume of carbon dioxid produced and the volume of oxygen absorbed, indicates the kind of food being burned at the time of the determination, and since by means of calorie tables the calorific value of one liter of oxygen absorbed by the body in the burning of these substances is known, the total heat production each hour can be calculated readily. The total number of calories must be divided by the surface area, a factor dependent on the patient's height and weight. The number of calories for each square meter of body surface each hour must then be compared with the normal standards of comparison which are dependent on the age and sex of the patient. For convenience, basal metabolic rates are expressed in percentages of the normal, and when the heat production is greater than the normal the percentage is plus, and when less than normal the percentage is minus.

A very important contribution was made by Du Bois (12, 13) in determining the heat production in normal controls. Rubner (24) had suggested that the heat production of an individual is proportional to his surface area. For the determination of the surface area Meeh (21) proposed the formula: Surface area in square centimeters=12.3 (a constant) $\times$ weight in grams$^{\frac{2}{3}}$. However, using the surface area obtained by this formula as a basis of comparison, the heat production of normal controls still showed quite wide variations, although not so great as when compared on the basis of weight alone. By exact measurements of the surface area of several bodies Du Bois demonstrated an error in the above formula due in greater part to the fact that the height of the subject was neglected. As a result of further studies Eugene F. Du Bois and Delafield Du Bois (12, 13) devised a formula based on height

and weight by means of which the surface area can be calculated with an average error of 1.7 per cent. This formula is:

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

Where A is the surface area in square centimeters, W is the weight in kilograms and H is the height in centimeters, and 71.84 is a constant. On the basis of this formula they then constructed a height-weight chart by means of which the surface area can be estimated at a glance. Du Bois (12, 13), using this new height-weight chart for the determination of the surface area in conjunction with his standards of normal basal metabolism with regard to age and sex, further showed that the metabolism of normal persons can be predicted with an accuracy of $\pm 10$ per cent. This fact has been confirmed both by Means (20) and by Boothby (19). Benedict (3) has severely criticized the method of predicting the heat production from the unit of surface area, maintaining "that the metabolism or heat output of the human body, even at rest does not depend on Newton's law of cooling, and therefore, is not proportional to the body surface." Harris and Benedict (15) in a very exhaustive treatise have reconsidered the entire problem of the prediction of the normal basal metabolic rate and show that by proper biometric formulas based on stature, body weight, and age (the same factors used by Du Bois), "results as good as or better than those obtainable from the constant of basal metabolism per square meter of body surface can be obtained by biometric formulas involving no assumption concerning the derivation of surface area, but based on direct physical measurements." Since their publication there has not been sufficient time to study in detail the fundamental accuracy of the two methods of prediction; we have, however, tabulated 404 determinations of the basal metabolic rate expressed in percentages above and below normal, using both the standards of Du Bois and of Harris and Benedict. The average rates of all the cases show that the rates obtained by Harris and Benedict's method are 6.5 points higher than those obtained by Du Bois' method. The parallelism between the results obtained by the two methods is strikingly shown by the fact that 195 of the 404 determinations are within $\pm 2.5$ of the average variation. Only 52 of the entire 404 rates deviate

more than 7.5 from the average variation. The comparative agreement, therefore, of the two methods is very satisfactory, indicating as it does the similarity of both methods of comparison, and supporting in a high percentage of the cases the clinical conclusions based on the Du Bois and Du Bois height-weight chart and the Du Bois normal standards for comparison.

The metabolism laboratory at the Mayo Clinic was opened, in March, 1917 by Boothby and Sandiford, under the clinical direction of Dr. H. S. Plummer, and in that year 1143 metabolic rates were determined on 549 patients. At that time the number of cases that could be studied in the laboratory in proportion to the number of thyroid cases at the clinic was relatively small. In consequence, considerable care was taken by Dr. Plummer to select typical cases of the various groups of thyroid disorders and with his permission this analysis of the metabolic rates in the exophthalmic goitre cases studied during 1917 is presented.

The basal metabolic rate is of the greatest value in thyroid disorders because it gives a very accurate mathematical index of the degree of functional activity of the thyroid gland. For example, in exophthalmic goitre the metabolic rate may rise well over 100 per cent above normal while in myxedema, with apparently complete cessation of thyroid activity, the rate falls to the region of 40 per cent below normal. In the milder cases of both groups the metabolic rate variations from the normal are proportionately smaller. On the other hand, beside thyroid disorders, there are no diseases that have so far been shown to have a constant and distinct variation from the normal in the basal metabolic rate except disorders of the pituitary gland, conditions of profound inanition, and fevers. However, an occasional case is met with in which there is a variation in the basal metabolic rate that at present cannot be explained or properly classified. Such variations are more frequent in patients with considerable evidence of nephritis or anemia. No definite instance of an increased basal metabolic rate has been found in that group of cases known as neurasthenia or chronic nervous exhaustion. The basal metabolic rate has proved, therefore, to be of great value

in the differential diagnosis of neurosis simulating hyperthyroidism and true hyperthyroidism.

In 182 cases of exophthalmic goitre before any treatment was instituted the average metabolic rate was +51 per cent, with an average pulse rate of 115. In 13 patients whose average metabolic rate, as outpatients, was +59 per cent, with an average pulse rate of 115, the average metabolic rate fell to +46 per cent, and the average pulse rate to 108 as a result of approximately one week's complete rest in bed. In 5 patients whose average metabolic rate, determined within two to five days after they entered the hospital, was +59 per cent and the pulse 118, after a further rest in bed of approximately one week's duration there was a definite improvement in their condition, as shown by a fall in the metabolic rate to an average of +48 per cent and pulse to 104.

The effect of a single ligation was studied in 16 cases. The basal metabolic rate taken after the patient had had several days' rest in bed and within five days before the first ligation was +54 per cent and the pulse 116. One week after the single ligation the average metabolic rate had decreased to +44 per cent and the pulse to 112.

The immediate result of ligation or thyroidectomy in hyperthyroidism is to cause at first a rise in the metabolic rate for a few days, followed by a gradual fall to a distinctly lower level on the average than that obtained preceding the operation. The curve of the basal metabolic rate on the average roughly parallels the pulse rate curve. The former is, however, a far more accurate index of the degree of hyperthyroidism than is the pulse rate, as the latter shows more individual and extraneous variations, for example, the irregularities of auricular fibrillation.

The effect of the second ligation is likewise a general improvement in the patient's condition as evidenced by a decrease in the metabolic rate. An average figure of any value on the immediate result of the second ligation in the patients in the 1917 series cannot be given, as practically no rates were obtained in the same case immediately preceding and following the second ligation. There is a very marked improvement in these patients when they return for their thyroidectomy

two to four months after the second ligation. In 22 patients (Table 1) there was an average decrease in the basal metabolic rate from +46 per cent to + 39 per cent, and in the pulse from 115 to 107 with a gain in weight from 46.4 to 54.5 kilograms in the determinations made a few days after the second ligation as compared with the data obtained after three months' rest at home and just previous to thyroidectomy. From the clinical history it is probable that the basal metabolic rate determined at the time the patients returned for operation after having had two ligations and three months' rest at home may not necessarily represent in all cases the period of maximum improvement produced by the two ligations and rest. A definite improvement from thyroidectomy in those patients who had had two ligations and a three months' rest was shown two weeks following operation by a decrease in the basal metabolic rate from +39 per cent to +16 per cent, and in the pulse rate from 107 to 89.

In another group of 19 patients (Table 2) with exophthalmic goitre in whom the preliminary basal metabolic rate varied between +13 per cent and +50 per cent, giving an average of +31 per cent with an average pulse rate of 104, and in whom a primary thyroidectomy was done without any other preliminary treatment, except for a short rest in bed, the basal metabolic rate fell, about two weeks after operation, to +5 per cent and the pulse to 84.

The general effect of the treatment adopted at the Mayo Clinic for severe cases of exophthalmic goitre may be illustrated, then, by the following data: In a group of 22 patients (Table 1) the average basal metabolic rate, before any treatment was instituted, was +66 per cent, with a pulse rate of 123. As a result of rest in bed and two ligations the rate in these patients before they went home had decreased to +46 per cent and the pulse to 115. The further improvement that occurred from three months' rest at home reduced the average metabolic rate to +39 per cent and the pulse rate to 107 and finally, after thyroidectomy and just before the patients were discharged from the clinic, the rate was +16 per cent and the pulse 89.

As will be noted, following thyroidectomy there is almost always a marked decrease in the basal metabolic rate within

Table 1

THE EFFECT OF TWO LIGATIONS AND THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE

| | Before treatment | | | Within five to nine days after second ligation | | | Three months after second ligation | | | Ten to thirty days after thyroidectomy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Wt. kg. | Pulse | B.M.R. Per cent | Wt. kg. | Pulse | B.M.R. Per cent. | Wt. kg. | Pulse | B.M.R. Per cent. | Wt. kg. | Pulse | B.M.R. Per cent. |
| 208970 | 50.1 | 139 | +101 | 38.1 | 118 | +36 | 52.2 | 95 | +50 | 56.8 | 69 | +15 |
| 201022 | 48.5 | 175 | + 98 | 40.9 | 124 | +49 | 51.5 | 114 | +26 | 48.1 | 107 | + 6 |
| 196042 | 46.0 | 138 | + 93 | 45.6 | 126 | +61 | 53.3 | 104 | +43 | 51.9 | 91 | +20 |
| 197894 | 46.7 | 128 | + 77 | 39.5 | 129 | +46 | 58.4 | 113 | +13 | 56.5 | 105 | + 1 |
| 192274 | 27.3 | 138 | + 76 | 40.1 | 120 | +53 | 42.7 | 129 | +58 | 40.9 | 92 | +27 |
| 194824 | 42.4 | 127 | + 76 | 41.6 | 123 | +58 | 51.9 | 110 | +34 | 51.4 | 100 | +13 |
| 210160 | 54.9 | 131 | + 75 | 57.7 | 124 | +60 | 63.9 | 105 | +55 | 63.0 | 82 | +21 |
| 196845 | 49.7 | 129 | + 74 | 47.5 | 146 | +78 | 55.3 | 129 | +68 | 56.0 | 120 | +58 |
| 215648 | 42.1 | 117 | + 73 | 43.4 | 115 | +54 | 48.0 | 82 | +12 | 53.7 | 74 | − 6 |
| 202677 | 60.5 | 98 | + 65 | 58.4 | 96 | +34 | 64.1 | 94 | +55 | 61.9 | 86 | +34 |
| 191713 | 49.0 | 87 | + 65 | 43.5 | 83 | +45 | 50.5 | 90 | +62 | 50.5 | 71 | +49 |
| 187927 | 48.5 | 121 | + 63 | 45.0 | 117 | +43 | 49.4 | 112 | +53 | 48.6 | 70 | + 3 |
| 189311 | 60.7 | 141 | + 60 | 49.9 | 88 | +27 | 58.3 | 105 | +43 | 56.0 | 44 | 0 |
| 199039 | 43.1 | 121 | + 56 | 36.6 | 123 | +50 | 48.2 | 100 | +50 | 48.6 | 76 | +14 |
| 200063 | 46.5 | 95 | + 55 | 45.9 | 110 | +58 | 46.9 | 121 | +54 | 46.6 | 97 | +20 |
| 199909 | 46.0 | 134 | + 55 | 46.0 | 127 | +42 | 52.8 | 132 | +52 | 53.0 | 88 | +13 |
| 136490 | 55.1 | 107 | + 55 | 44.2 | 104 | +41 | 65.5 | 82 | +11 | 65.3 | 85 | 0 |
| 194306 | 43.2 | 126 | + 53 | 42.0 | 124 | +48 | 50.1 | 117 | +21 | 49.5 | 105 | + 9 |
| 197356 | 58.5 | 99 | + 52 | 53.0 | 80 | +13 | 60.0 | 77 | + 1 | 56.9 | 75 | − 2 |
| 191257 | 60.5 | 130 | + 50 | 56.7 | 123 | +45 | 61.2 | 110 | +34 | 58.5 | 117 | +16 |
| 209717 | 55.6 | 133 | + 47 | 54.0 | 141 | +37 | 59.0 | 127 | +39 | 57.0 | 88 | +16 |
| 190576 | 53.0 | 86 | + 31 | 51.6 | 92 | +31 | 55.6 | 106 | +25 | 58.3 | 106 | +19 |
| Average | 49.5 | 123 | + 66 | 46.4 | 115 | +46 | 54.5 | 107 | +39 | 54.0 | 89 | +16 |

two weeks after the operation and, as a rule, there is still further improvement in the succeeding months, just as is seen to occur in the interval after the second ligation. Occasionally, a varying degree of hyperthyroidism may persist, as shown by

Table 2

THE EFFECT OF PRIMARY THYROIDECTOMY ON THE BASAL METABOLIC RATE IN EXOPHTHALMIC GOITRE

| | Before treatment | | About two weeks after operation | |
|---|---|---|---|---|
| Case | Pulse | B. M. R. Per cent | Pulse | B. M. R. Per cent |
| 214581 | 88 | +50 | 70 | +19 |
| 196806 | 109 | +45 | 93 | + 3 |
| 202992 | 107 | +45 | 92 | + 5 |
| 200219 | 145 | +42 | 115 | +12 |
| 201229 | 102 | +40 | 75 | +14 |
| 202481 | 105 | +39 | 68 | + 1 |
| 202527 | 112 | +36 | 92 | +15 |
| 194686 | 97 | +35 | 75 | + 1 |
| 212298 | 108 | +34 | 91 | + 5 |
| 202232 | 113 | +32 | 118 | +32 |
| 203326 | 127 | +30 | 89 | +10 |
| 3396 | 101 | +29 | 83 | +13 |
| 198725 | 99 | +27 | 67 | 0 |
| 196664 | 79 | +21 | 58 | −11 |
| 203291 | 87 | +18 | 73 | − 6 |
| 199740 | 95 | +18 | 69 | − 7 |
| 217150 | 99 | +16 | 85 | − 5 |
| 215895 | 118 | +16 | 98 | − 9 |
| 208637 | 89 | +13 | 84 | + 6 |
| Average | 104 | +31 | 84 | + 5 |

an elevated basal metabolic rate. In these cases a second (and rarely a third) thyroidectomy is indicated.

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## STRUCTURE OF THE THYROID AND ITS QUALITATIVE VARIATIONS: A REVIEW.

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A promising field for productive investigation is that of histochemistry. Although the tinctorial reactions by which cell structure is commonly studied amount, in effect, to qualitative chemical analyses, this fact has been little stressed. This possibly is due to the condition that investigators who utilize tissue stains are usually interested primarily in morphology. Accordingly, stains are chosen primarily for their ability to reveal structure and relative little attention has been paid to the fundamental chemistry involved.

There now are in use a large number of analytic procedures which depend upon qualitative color reactions for determining the composition of body products. Many of these would lend themselves to the analysis of cell components. Such microanalyses might well add much to our knowledge of conditions in the endocrine organs and their variations in health and disease.

An interesting series of studies in this field has been made by Prof. Buscaino of the San Salvi Clinic at Florence. (1)

Several mental diseases (epilepsy, paresis, etc.) in which a true condition of dysthyroidism exists, have not afforded conclusive histo-pathological findings in the thyroid, because, Buscaino remarks, the research was turned to the size of the acini, to the quantitative variation of the colloid, of the interalveolar connective tissue, to the proliferation of the epithelium and so on, instead of to qualitative variations of the colloid and of the elements apt to be found in it. Buscaino's object in this study has therefore been to look for such qualitative variations and see if it were possible to give an anatomical basis to the described conditions of dysthyroidism.

I. It was found that a first variation consists in real crystals (octahedral) in the mass of the colloid. They are not soluble in water, in alcohol, in acetone, in sulphuric ether, in mineral acids, in acetic acid or in alkali. They do not take the Sudan III stain. Therefore they are neither inorganic, nor fats, nor carbohydrates. With the xanthoproteic reaction, Millon's, Lieberman-Wurster's and Axenfeld's tests they appear to be of protein substance, and to contain, besides other groups, aromatic groups with oxyphenylic structure. These crystals vary in size

(1) Buscaino (V. M.) Rivista di Patologia nervoso e mentale (Firenze), 1914-15, **19**, fasc. 7-8; **20**, fasc. 2, 3, 4, 5, 10.

and are found in very few thyroids—usually in the normal, very seldom in the chromophil colloid.

II. There are also calcium oxalate crystals, which never appear in the octahedral form. They are to be found in the colloid, more or less close to the epithelium. They are not found in all thyroids and their number varies greatly.

III. Other crystals of organic nature have also been found in the colloid. It has only been determined that they are not amino-acid, uric acid, hippuric acid or xanthin. They have been found only once in a case of Basedow's disease.

IV. The colloid itself may vary; one of its modifications we call "chromophil colloid" on account of its reacting to several stains (Niblau, Mallory's reaction) in a different way than the normal colloid. It may fill the acini or appear only as an admixture with the normal colloid in a small amount. Characteristic is its way of never adhering to the epithelium, which is usually low and often degenerated.

V. The "Sudanophil" is another variation of the colloid. With the Sudan III and Delafield hemotoxylin the normal colloid is bluish and the chromophil intense blue, while the Sudanophil is reddish yellow. It hardly gives a positive xanthoproteic reaction and does not give the Millon's. It is found in enlarged acini and looks different from the normal and the chromophil colloid. It can be found in the interalveolar spaces,—very often where there are hemorrhages, which seem due to its toxic action on the walls of the blood vessels.

VI. The colloid may also appear in a degenerated form as broken in fragments more or less broad, with regular margins, mixed with detritus of epithelial cells.

VII. Granules of neutral fats and lipoids are also found which, stained with Sudan III, become intensely red-orange. They are believed to increase with the age of the subject. They are never found in the new born. They begin to show during early youth and their maximum is reached between 70 and 85. They are increased in senile dementia.

VIII. Abnormal fatty substances are also found as doubly refracting epithelial granules in the acinar epithelium; as ethers of cholestrol in the colloid and, finally, under conditions when the whole epithelial protoplasm takes the Sudan III, a reaction due to the presence of true lipoids, which are never found in the normal condition.

IX. Dark granules are also found in the alveolar epithelium which, by their reactions, are shown to belong to neither fats, proteins nor carbohydrates. It is believed that they are of melanotic pigment.

X. Granular inclusions are often found in the sudanophil colloid, not necessarily accompanied by hemorrhage; they ap-

pear when acini are lacking. These granules may be of three kinds, sometimes all together in one cell: (A) Sudanophil granules, mostly constituted of neutral fat and lipoids; (B) Black granules very similar to the "dark granules" (IX);

XI. (C) Thiophil granules (becoming violet-red with thionin) which are very likely protein.

XII. Other substances may appear in the interacinar spaces colored yellow-red with Sudan III, like the sudanophil colloid.

XIII. Finally, infiltration of lymphocytes has been found. This is supposed to be due to persistence of the thymus and status lymphaticus.

As regards lymphocytosis in connection with thyroid disorders, the author claims that the leukopenia observed in cases of Basedow's disease, with increase of the mononuclears, is not characteristic of this disease, but is found in almost all abnormal conditions of the thyroid. This condition seems to be due to a reaction on the part of the thymus and of the lymphatic system to any form of dysthyroidism; in other words, whenever an infectious toxemia can be excluded in cases of lymphocytosis it is to be considered as an expression of an endocrinic toxemia, i.e., a functional variation of thyroid, thymus and lymphatic systems.

In cases of simple goitre Buscaino found dilated acini, sudanophil colloid and hemorrhages. No protein crystals, no, or very little, chromophil colloid, and no calcium oxalate crystals were found.

In cases of Graves' disease, extreme diminution of the normal colloid, the presence of sudanophil and chromophil colloid, and absence of protein crystals and of calcium oxalate were noted.

From the post-mortem examination in cases of epilepsy, paresis, dementia precox, senile and arteriosclerotic dementia and amentia, the author came to the conclusion that all these forms (in which the patients showed more or less evidence of dysthyroidism while living) show the presence of chromophil colloid. Without being pathognomonic for any of these forms, such colloid seems to have a special importance in cases of paresis.

The crystals of calcium oxalate show only an active participation of the thyroid in calcium metabolism. They were found mostly in cases of dementia precox.

The octahedral protein crystals have a special significance in epilepsy. It was found that the cases of essential epilepsy showed signs of dysthyroidism; microscopic examination disclosed chromophil colloid and octahedral crystals of protein. In cases of symptomatic epilepsy the findings were negative.

To summarize: Chromophil colloid and sudanophil colloid were found in nearly all cases of mental disease which offered, during life, symptoms of dysthyroidism; the calcium crystals were seldom found and then, almost exclusively in dementia precox; the octahedral protein crystals were found in cases of epilepsy or other diseases with epileptic seizures.

In a study of the corpuscular variation of the blood in epilepsy and the psychoses the author could find variations of the formula in almost all forms. But the variations were not so constant as to afford any definite pathognomonic data. He found, though, that in epilepsy (in two-thirds of the cases) there was a very definite eosinophilia. Such condition of the blood seems always to be determined by disintegration and successive parenteral penetration of foreign or homologous proteins into the blood.

Owing to the frequency of eosinophilia in epilepsy, to the finding of crystals of protein in these cases and to the conclusions drawn by Schlecht, Schwenker, Ahl and Schittenhelm that the eosinophilia has a great importance in the phenomena of anaphylaxis, representing as it does the reaction of the organism against foreign or homologous protein, when it enters parenterally into the circulation, the author was brought to look for any possible analogy between epilepsy and anaphylactic shock, and to see if epileptic attacks could not be considered as an anaphylactic reaction of the organism against the penetration of abnormal protein from the thyroid. He therefore draws a parallel between the symptoms offered by these two conditions (epilepsy and anaphylaxis) which leads him to the conclusion that the "epileptic seizures offer the symptoms of an anaphylactic crisis, determined by intoxication of either peptones or substances resembling peptones in their protein genesis and in their toxic effects.

Of course not all the cases having epileptic attacks show protein crystals (as has been noted in a previous paragraph in regard to the difference between essential and symptomatic epilepsy) and not all the cases showing protein crystals have epileptic seizures. But in this case we must not forget that first, the eosinophilia, when present, can counteract the epileptic attack; second, that to obtain an anaphylactic condition there is required a certain amount of toxic substance which, besides, in its repeated action must enter the circulation at not too brief intervals in order to permit sensitization of the organism.

In studying paresis Buscaino found in every case the presence of chromophil colloid and came to the following conclusions:

1. Among the anatomo-pathological findings of dysthyroidism in paresis the chromophil colloid is the expression of a qualitative alteration of the thyroid function, leading to intoxication

of the organism and ultimately to hypofunction of the thyroid. 2. The chromophil colloid is not the cause of the disease, but an effect of it. 3. Its formation seems to be an effect of the lesions which determine the paralytic process and consequent formation of special cerebral toxic substances. 4. The chromophil colloid has been found in all cases of paresis studied. 5. The forming of the chromophil colloids is the starting point of the alteration of metabolism through alteration of other endocrine glands. There may be a predisposition to favor the incidence of thyroid complications. 6. Paresis is a cerebral spirochetosis which determines dysthyroidism which in its turn brings about organic decay. 7. Also, in paresis the epileptic seizures represent anaphylactic crises. In all these cases protein crystals have been found. 8. The association of thyroid treatment with specific antiluetic treatment helps to diminish the intensity of the Wassermann reaction (blood and spinal fluid).

Finally, a study was made of the possible alterations in the blood serum in connection with the presence in the thyroid, and probable introduction into the circulation, of the protein crystals and of the chromophil colloid, which both were proved to contain a substance with oxyphenylic structure (oxybenzoic).

Believing that the organism usually reacts against the presence of abnormal substances with the production of specific ferments, an attempt was made to determine if there were formation in normal serum of phenolysins for substances with cyclic groups with oxyphenylic structure; and if so, what kind of variation exists in cases where such substances were found in greater amount, as in epilepsy and paresis.

The ability of the blood serum to bring about oxidation of hydroquinon was investigated. Although the reaction was positive, the effect was not due to a real ferment, since this "phenolysin" kept its power after heating to 100° C. for a few minutes, and after precipitating the blood proteins with 96% alcohol filtering and boiling for ten minutes.

The conclusions were as follows: In normal conditions the human blood serum has in vitro a powerful oxydizing action on hydroquinon, due to a substance soluble in 96% alcohol and thermostable; this power increases a great deal in cases of paresis, and to a less extent in epilepsy—that is, the oxydizing power is more marked during the interacessual periods, less before the seizure.

Owing to the fact that in these two diseases in which cyclic groups with oxybenzolic structure are found, the blood serum offers an increased oxydizing power toward such substances, the author asks if it might not be possible, with the above quoted reaction, to recognize in vivo the presence of these qualitative thyroid variations.

## BOOK REVIEW

### PATHOLOGICAL PHYSIOLOGY OF THE THYROID AND THE THYMUS IN RELATION TO INFECTIONS (FISIOPATOLOGIA DELLA TIROIDE E DEL TIMO NEI RAPPORTI CON LE INFEZIONI). Mario Barbara, R. Università di Palermo. Societa Editrice Libraria, Milano, 1918, pp. 260.

The book is based on an extensive consideration of the literature, a long bibliography of which is included, together with personal researches by the author. In the introduction are considered the relations which exist between the endocrine glands and infections and the relations of the thyroid and the thymus.

The first section of the thesis, proper, takes up a study of the thyroid in relation to infections. The gland has a defensive action against such. After thyroidectomy animals show a considerable degree of diminution of effectiveness of the immunizing mechanisms, as complement, bacteriolysins, opsonins and phagocytic power of the leucocytes. Through its relation with the liver and kidneys also the thyroid affects resistance. Histologic changes in these organs can be demonstrated after disturbances of thyroid function as in myxedema, cretinism and exophthalmic goitre, as well as after acute and chronic infections, which the author believes particularly influence the thyroid. In these conditions he has found either progressive thyroid metamorphosis (epithelial cell proliferation, increase of secretory granules and of colloid, accumulation of lymphocytes, etc.) or of regressive metamorphosis manifested as sclerosis, atrophy, alterations of the colloid and epithelial degeneration. These changes in turn lead to thyrogenic symptoms which vary more or less in accordance with the nature of the infection.

In the second part of the book the author summarizes a series of studies on thymectomised guinea pigs, as regards the phagocytic power of the leucocytes, and the complementary, opsonic and agglutinating power of the blood serum. It is concluded that in the thymus originate substances which stimulate phagocytosis; such substances can be demonstrated in extracts of the gland. It either forms complement or through its hormone influence on other structures stimulates complement formation. Similarly, it can be shown to form or augment the formation of opsonins, but apparently has no essential part in the formation of agglutinins. Neither does it play a significant role in the resistance to chloroform poisoning, as has been previously claimed. Thymectomy results in a loss of balance among the defensive mechanisms of the body but, later, compensatory changes take place in other structures to restore the balance. The opsonic power of the serum was found, however, to remain permanently lowered after thymectomy.

Anatomically, it was found that, following infections, the thymus reacts as do lymphoid organs and that ordinarily atrophy results. On this basis the question is raised whether primary thymus insufficiency may not be one of the conditions predisposing to infections. It is pointed out that in such conditions as pregnancy and starvation, when infection is more prone to occur, thymus atrophy is seen. As signs pointing to thymus insufficiency Barbara mentions trophic changes in the skin, cachexia, muscular atrophy and weakness, metabolic perturbations—especially of calcium metabolism in tuberculosis, etc. He describes the syndromes of "athymism," "hypothymism," status thymolymphaticus and the exudative diathesis of Czerny and then the corresponding opotherapy.

Thymic dysfunction is ascribed partially to infections in the parents. Such dysfunction leads to greater liability to some infections than to others. For instance, in Barbara's experience, tuberculosis is rare in individuals having thymus hyperplasia whereas, conversely, in cases of active tuberculosis, thymic atrophy is marked. Such atrophy, it is claimed, cannot in many cases be ascribed to the general wasting effect of the disease, being noted at a stage when time has not sufficed for such effect. It appears to the reviewer, however, that there is nothing so definite in the thymic changes recorded as to force upon us the conviction that they are specifically causal rather than a part of the general effect of disease in the organism.

Other objections to Barbara's conclusions might be offered. The inflammatory changes of the thyroid in acute infections, and sclerosis, atrophy and degeneration in chronic diseases would rather point to a non-specific reaction. In regard to the thymus, if we consider it as a lymphoid organ, it is evident that, in case of its suppression, there comes a greater strain on the lymphatic system; this may account for the lowered resistance of the organism as well as its subsequent recovery of balance after a certain length of time. Furthermore, even admitting that the thymus is not precisely a transitory organ, still its size and function undergo with age a remarkable diminution, but there is ordinarily no consequent impairment of organic resistance. The early disappearance of the thymus seems to be an occurrence common to all wasting diseases, rather than a peculiarity of tuberculosis and, as yet, we cannot state whether the disappearing thymus opens the door to the infection, or the infection makes the thymus disappear.

Notwithstanding the several points, which may be open to discussion, this work of Prof. Barbara shows a thorough knowledge of the literature and his diligent research opens new fields to the activity of investigators.

G. VERCELLINI.

# ABSTRACTS

**(ADRENAL) Sergent's "white line" in suprarenal insufficiency.** Anon, Lancet (Lond.), 1918 (ii), 713-714.

An abstract of an article by Prof. Massalongo in which he describes the attempt to produce the white line in 400 cases of various diseases. The line was found in an unequivocal form in only 300 cases; the majority of these were typhoid or paratyphoid. Because of its rarity, inconstancy and transiency and because of its presence or absence in equal proportion in cases where changes in the suprarenal capsules are indisputable, he credits the white line with only a relative diagnostic importance and does not consider it as pathognomic. It has, however, some value from a prognostic point of view, since its maximum frequency is met with in cases of serious import with almost invariably a fatal issue. See Endocrin., 1917, **1**, 18-23.—L. G. K.

**(ADRENALS) A case of Addison's disease with unusual onset.** Anon., Guy's Hosp. Gaz. (Lond.), 1918, **32**, 286.

Report of sudden collapse and death of a patient three months after a radical mastoid operation. Previous to the collapse no particular abnormalities could be detected in any system. The collapse was accompanied by a fit, with twitchings of the limbs on the right side, and later, with rigidity on same side. This was followed by unconsciousness. Rupture of a cerebral abscess was thought of, but the cerebro-spinal fluid was clear. The patient died next day and at autopsy the only abnormality found was enlargement of the suprarenal bodies. These were 2½ inches long and ½ inch broad. On section no cortex was to be seen. In the medulla there were large caseating nodules; no normal suprarenal tissue was seen at all. The only pigmentation was a slight coloration on the internal aspect of the thigh.—F. S. H.

**(ADRENALS) A case of Addison's disease from the surgical wards.** Anon., Guy's Hosp. Gaz. (Lond.), 1918, **32**, 286-287.

A patient had a septic tarsus (tubercular), the X-ray showing well marked bone destruction and no bone formation. The previous history revealed broncho-pneumonia with slow

recovery, total alopecia and a feeling of lassitude during the past three years. Preliminary to amputation, phthisis was found in right lung. Though reacting unfavorably to the continued anesthetic he came out and did well for 18 hours, but suddenly collapsed and died of cardiac failure in about ten minutes. The autopsy demonstrated an extensive tubercular involvement of the whole body. Particularly to be noted were the enlarged adrenals filled with typically caseous tuberculous material.—F. S. H.

**ADRENALS, Nervous control of the secretory function of the—(Die Innervation der Nebenniere durch den Splanchnicus).** Asher (L.), Arch. f. d. ges. Physiol (Bonn), 1917, **166,** 372.

Asher points out, against the criticism made by Popielski, that in his experiments on the effect of splanchnic stimulation pressure upon the adrenals was carefully avoided. He, therefore, still maintains that the secretory function of the adrenals is controlled through the splanchnic nerve.—E. U.

**(ADRENAL) The action of adrenalin on blood pressure (Die Blutdruckwirkung des Adrenalins).** Bauer (J.), Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1217.

On page 955 of the same journal Dresel published an article in which he stated that the blood pressure reaction after adrenalin injection affords a good criterion to distinguish normal individuals from those having vagotonia and sympathicotonia. Bauer discusses Dresel's article and comes to the conclusion that the method indicated has no value. But we do not need a method for this purpose, as, also according to Bauer, the existence of "vagotonia" and "sympathicotonia" has never been proved and is extremely improbable.—J. K.

**(ADRENALS GONADS) Tumor of the adrenals and destruction of the gonads in a man (Nebennierentumor und Geschlechtsdrüsenausfall beim Manne).** Bittorf (A.), Berl. klin. Wchnschr., 1919, **56,** 776.

Description of a remarkable case. A man of 26 years noticed that his sexual desires had diminished. The testicles became atrophic and at the same time a tumor developed in the abdomen. The breasts hypertrophied, resembling the female type. The urine contained red and white blood cells, casts and large cells. The skin showed but little pigmentation. The diagnosis, hypernephroma, was confirmed by postmortem examination.—J. K.

**(ADRENAL) Acute suprarenal disturbance in the course of hereditary syphilis with a polymorphic erythema (Surrénalite aiguë dans le cours d'une syphilis secondaire et á la suite d'un èrythème polymorphe).** Blum, Bull. Soc. Méd. des Hôp. (Paris), 1916, **40**, 1767-1774.

A case report.—A. L. T.

**(ADRENAL) Influenza as a cause of acute Addison's disease (Grippe als Auslösungsfaktor von akutem Addison).** Brunecke, Therapeutische Monatshefte (Berlin), 1919, **33**, 354.

A remarkable case. A girl of 12 years with tuberculosis of the lungs and of the ulna gets influenza. Acute Addison's disease with pigmentation of the skin (not of the mucous membranes), enormous weakness, apathy and a blood pressure of 70 mm. develops. The child becomes so extremely weak that she cannot sit up alone in bed. Following treatment with "partial antigens" (Deyke-Sluck), the blood pressure rose, the child regained strength, the pigmentation began to disappear and after some time the child was able to play again in the garden.—J. K.

**ADRENAL, enlargement of—in starvation.** Byrne (C. H. C.) Brit. Med. J. (Lond.), 1919 (ii), 135.

The author noted that in a series of eight autopsies on soldiers who had died from underfeeding in a German prison camp, the adrenals were enlarged to almost one and a half times the normal size. The enlargement seemed, from naked-eye appearance, to be mostly in the cortex.

The suggestion is made that the adrenals had hypertrophied to counteract the low blood pressure produced through insufficient nourishment. The author is apparently unfamiliar with the more recent work on the subject of the effect of the adrenals on blood pressure.—L. G. K.

**(ADRENAL) On the clinical evidence of involvement of the suprarenal glands in influenza and influenzal pneumonia.** Cowie (D. M.) and Beaven (P. W.), Arch. Int. Med. (Chgo.), 1919, **24**, 78-88.

Necrospy reports indicate hypoplasia and evidence of suprarenal dysfunction following influenza. The occurrence of suprarenal dysfunction in influenza and influenzal pneumonia may be regarded as indicated by the cardinal symptoms—asthenia and low blood pressure—the characteristic rise in blood pressure following the prolonged administration of epine-

phrin, and the prolonged blood pressure curve following epinephrin injections. Further, the prolonged blood sugar curve after injection of epinephrin and the prolonged sugar curve after the ingestion of glucose also indicate an endocrinal disturbance in influenza. Hypoglycemia is not present in influenza or influenzal pneumonia as has been found to be the case in certain diseases of endocrinal origin. The administration of epinephrin is of no use in the treatment of influenzal cases. Possibly the proper method of administration has not been evolved; subcutaneous injections of epinephrin is valueless.

—H. W.

**(ADRENAL PINEAL HYPOPHYSIS) The effects of some glandular extracts upon the contractile vacuoles of Paramecium caudatum.** Flather (M. D.), Biol. Bull. (Woods Hole), 1919, **37**, 22.

This paper describes a series of experiments to determine the influence of some glandular extracts upon the contractile vacuole of Paramecium caudatum. An exhilaration of pulse frequency was produced by solutions of pituitary substance, adrenalin and pineal extract, the extent and duration being dependent upon the concentration of the solution. The greatest exhilaration was produced by pituitary substance, the least by pineal extracts. The author believes that the stimulation is produced, not by the direct effect of the autacoid principles upon the vacuole itself, but by the indirect effect of heightened metabolism in the entire organism. The vacuoles become more active in compensation for this increase in metabolism. A review of the literature giving the nature and function of the contractile vacuole is given. (Author's abstract.)

Shumway had previously shown that thyreoid substance placed in cultures of Paramecium also will hasten metabolism, but he called the activating principle of the thyreoid a "dissimilatory" hormone. The idea expressed by the present writer is probably more accurate than that of Shumway.

—E. R. H.

**(ADRENAL) Da asthenia suprarenal.** de Fonseca (J. M.), Arch. Brasil. de Méd., 1919, **9**, 149-163; Physiol. Abst., **4**, 340.

The author by means of electric stimuli exhausted the gastroenemius muscles of frogs and determined that by the injection of adrenin into the tissue mass the muscle could be immediately restored. Curare injected simultaneously with adrenin at once loses much of its effect. From these results and those of other investigators de Fonseca accepts the theory

that adrenin neutralizes the products of muscular activity, preventing their curare-like effects. Similarly, the asthenia observed in certain pathologic conditions is regarded as due to a failure of the adrenal glands to secrete adequately.

—R. G. H.

**(ADRENALS) Syndrome of incipient or abnormal Addison's disease with presence of "white line of Sergent" (Syndrome d'addison fruste avec présence de la ligne blanche).** Mussio Fournier (J. C.) and Sergent (E.) Bull. Soc. Méd. des Hôp. (Paris), 1919, **43**, 207.

An atypical case of Addison's disease, characterized by acute abdominal pains, pigmentation on skin areas normally subjected to pressure and in the sclera and buccal mucosa. A history of scrofulous glands existed. There was a high degree of sugar tolerance, failure of appearance of glycosuria after ingestion of 200 gm. of glucose, or after injection of 3 mg. of epinephrine.

Treatment: 40 gtt. adrenalin per day was followed by disappearance of vomiting, diarrhoea, and for the most part pain and fall of heart rate from 120 to 80. However, the heart continued to be very unstable as, under effort, the rate would rise to 130 to 140, yet without serious fatigue or feeling of weakness. The "white line" of Sergent no longer appeared.

—A. L. T.

**(ADRENAL) The relation between central nervous system, adrenals and carbohydrate metabolism. A discussion of the problem: Sugar puncture and adrenals (Über die nach zentraler Reizung zur Störung des Kohlehydratstoffwechsels führenden Vorgänge. Eine kritische Studie zur Frage: Zuckerstich und Nebennieren).** Kahn (R. H.), Arch. f. d. ges. Physiol. (Bonn), 1917, **168**, 326.

A discussion of experiments relating to the role of the adrenals in the glycogen mobilization occurring after sugar puncture. It was concluded that both the glycolytic ability of the liver cells and the adrenalin excretion by the adrenals are controlled, through the splanchnic nerve, by the central nervous system. Sugar puncture makes the liver cells more sensitive to the action of adrenalin and increases adrenalin secretion. Therefore a slight increase of the glycogen mobilization may take place after sugar puncture also in the absence of the adrenals, while in their presence glycogen mobilization after sugar puncture is far more marked. The mobilization of sugar after sugar puncture demonstrates one of the physiological

activities of the adrenals, the function of which is probably to regulate carbohydrate metabolism under the control of the central nervous system.—E. U.

**ADRENAL glands, The effects of a scorbutic diet on the—.** McCarrison (R.), Brit. Med. J. (Lond.), 1919, (ii), 200.

The effects of a scorbutic diet on the adrenal glands were studied in guinea-pigs fed on crushed oats and autoclaved milk. The naked-eye changes consist in enlargement of the adrenals with increase in their weight and in congestion. The weight of the adrenal glands of animals dying in consequence of the scorbutic diet is approximately double that of health. The increase in weight is even more marked when the weight of the glands is calculated per kilo of original and final body weights.

Microscopically hemorrhagic infiltration and disintegration of the cellular elements of the cortex and medulla are seen. The areas of hemorrhagic infiltration are situated around the periphery of the cortex. These changes are regarded as pre-scorbutic, since they occur in animals exhibiting no clinical evidences of scurvy during life.

The adrenalin content of the glands (estimated by the method of Folin, Cannon and Dennis) is less than half that present in healthy guinea-pigs, in spite of the greater weight of the organs.

It is pointed out that normally the total adrenalin per gram of gland in pigeons is approximately ten times greater than in guinea-pigs. The author has previously shown that a great increase in the adrenalin content of the adrenals occurs in pigeons deprived of accessory food factors of all classes (Endocrin. 1919, **3**, 201-2). He now finds that when vitamines of the "A" class in the form of fresh butter are added to the diet, an increase of adrenalin does not as a rule occur. He therefore concludes that lack of accessory food factors of the "A" class causes excessive production of adrenalin associated with oedema in aves, and that in guinea-pigs the lack of factors of the "C" class causes diminished adrenalin production associated with hemorrhage into the body tissues.

L. G. K.

**The ADRENAL glands and toxi-infections.** Marie (A.), Ann. inst. Pasteur (Paris), 1918, **32**, 97-110.

Tetanus toxin can be rendered innocuous for mice by mixture and incubation with adrenalin. Simultaneous injection of adrenalin with the toxin does not, however, prevent the onset

of symptoms. Mixture and incubation must precede injection. Such mixtures retain the power of producing specific antitoxin on injection into rabbits. Tetanus toxin, non-diffusible in the pure state, dialyzes after contact with adrenalin, the dialysate being capable, on injection, of producing specific antibody, but not of causing tetanus.—Chem. Abst. **13,** 3233.

**(ADRENAL) A study of hyper-adrenalism; its influence in producing congenital pyloric hypertrophy and subsequent obstruction.** Pirie (G. R.), Lancet (London), 1919, (ii), 513-515.

The author suggests that congenital pyloric hypertrophy is the result of spasm primarily due to hyper-adrenalism before birth, and that other subsidiary post-natal causes determine the persistence or recurrence of the spasm. This condition is supposed to be due to a lack of balance between the secretions of the various endocrinic organs in the process of their development and involution, which may result either in a relative or an absolute hyper-adrenalism.

Phimosis is mentioned as one cause contributory to the pyloric hypertrophy and the phimosis is supposed to be due to a precocious sexual development resulting from slow involution of the suprarenals. Hyper-adrenalism is also suggested as a cause of pancreatic insufficiency. The consequent absence or reduction of the alkaline pancreatic secretion, which normally neutralizes the acid chyme in the duodenum, allows the pylorus to remain closed longer than usually. This again tends to produce hypertrophy of the sphincter muscle.

The hypothesis is entirely speculative and no real evidence is offered in its support. The author evidently forgets that in fetal life the cortex rather than the medulla is hypertrophied when he advances the large size of the fetal adrenal gland as a possible cause of hyper-adrenalism.—L. G. K.

**(ADRENAL) Adrenin and Adrenals. 1. The Presence of adrenin in the venous blood of the adrenals the result of pressure exerted upon the adrenals. (Adrenalin und Nebennieren. 1. Komprimierung der Nebennieren und Adrenalin.)** Popielski (L.), Arch. f. d. ges. Physiol. (Bonn), 1916, **165,** 565.

The fact that adrenalin is found in the venous blood of the adrenals is no proof of the adrenalin being the product of a secretory activity of these glands. First, it seems that adrenalin occurs, not as free secretion, but enclosed in the parenchyma cells of the adrenals. Second, these cells can be pressed through the walls of the vessels by means of the

slightest pressure exerted upon the adrenals, and such a pressure cannot be avoided in handling the glands. P.'s experiments show that compression and even the slightest touch upon the adrenals is sufficient to make adrenalin appear in the circulation. In dogs, after cutting the spinal cord in the region of the medulla oblongata, the splanchnic and the sympathetic nerves, pressure exerted upon the adrenals resulted in a considerable increase of the blood pressure, which was the higher the more pressure there was exerted and the longer it lasted. Defibrinated blood obtained from the circulation of the dog after the pressure experiment increases the blood pressure of the rabbit injected with the blood, and, added to Tyrode's solution, it abolishes tonus and contractions of the isolated intestine. The possibility that the increased blood pressure was the result of a stimulation of the peritoneal membrane was excluded by cutting the medulla oblongata and the splanchnic. P. finds that stimulation of the sympathetic, even in the absence of adrenalin, causes a rise of the blood pressure similar to that resulting from compression of the adrenals; the action of the sympathetic is independent of adrenalin. Yet, in the above described experiments the rise of the blood pressure was actually due to compression of the adrenals and not to stimulation of the splanchnic nerve; this was made sure by especially careful experimentation. If the aorta is compressed for one minute, the pressure in the carotid artery rises very high; sudden removal of the clamp from the aorta results in the production of a rapid flow of blood through the adrenals, which would carry adrenalin accumulated in the vein of the adrenals into the general circulation and make the blood pressure rise. No rise, however, took place in this experiment. It was concluded that adrenalin is not an internal secretion of the adrenals, since it is not excreted by the adrenals and is found in the circulation only when pressed out of the parenchyma by compression of the glands. The function of the adrenals is to detoxicate the blood by removing adrenalin and storing it in the parenchyma of the glands in the form of an unstable compound. If the cells containing this compound are pressed through the walls of the vein of the adrenals, the adrenalin can be broken away from this compound by the $CO_2$ of the venous blood.—E. U.

**(ADRENAL) Adrenin and the Adrenals. II. Normal blood, nervi splanchnici and adrenin (Adrenalin und Nebennieren. II. Normales Blut, Nn. splanchnici und Adrenalin).** Popielski (L.), Arch. f. d. ges. Physiol. (Bonn), 1616, **165**, 581.

Blood, taken from the vena cava inferior by means of a

device which secured blood coming from the adrenals only and yet did not permit of compression of the adrenals, was carefully defibrinated and injected through the vena jugularis of the animal from which it was taken. It did not raise the blood pressure, but on the contrary, like defibrinated blood of all organs, decreased it. The adrenals, therefore, do not excrete the adrenalin into the circulation. In order to determine whether or not the sympathetic nerve controls secretion of adrenalin, the sympathetic was stimulated under conditions which avoided any compression of the adrenals. Such stimulation caused no excretion of adrenalin; blood taken from the animal during stimulation of the nerve did not increase blood pressure if injected into circulation. P. criticizes severely Cybulsky's experiment, according to which adrenalin acts upon the central nervous system, and claims that its action is purely peripheral. But, since under normal conditions the tonus of the vessels is actually controlled by the central nervous system, P. thinks that adrenalin has nothing to do with normal maintenance of the tonus of the blood vessels.—E. U.

**(ADRENAL) The excretory innervation of the adrenals. A critique of the work of Asher, Elliot, Cannon and de la Paz, Anrep, Tscheboksareff, and Kahn and Eiger (Über die sekretorische Innervation der Nebennieren. Kritische Bemerkungen über die Arbeiten von, Asher, etc.).** Popielski (L.), Arch. f. d. ges. Physiol. (Bonn), 1918, **170**, 245.

A criticism of various papers, maintaining the standpoint that adrenalin found in the blood during stimulation of the splanchnic nerve entered the circulation, not because of the stimulating effect of the splanchnic upon adrenalin excretion, but because it had been forced from the adrenals into the circulation by pressure exerted upon the glands in the course of the experiment.—E. U.

**(ADRENAL) Addison's disease of war (L'addisonisme de guerre).** Ramond (F.) and François (R.), Bull. Soc. Méd. des Hôp. (Paris), 1917, **41**, 1001.

From a series of studies the authors conclude that it is extremely probable that Addison's disease as observed in, and initiated by, stress of war is in all cases ultimately tubercular in origin. This tuberculosis may be secondary to any other latent or active focus, and is but rarely primary.—A. L. T.

**(ADRENAL) A case of hypoadrenia simulating intestinal obstruction.** Rashbrook (H. M.) and Carter (F. W.), Lancet (Lond.), 1918, (ii), 240.

A case is described of tuberculous destruction of the suprarenal glands, the symptoms of which were repeated attacks of epigastric pain and vomiting, accompanied by constipation. The patient was weak and had a temperature of 95° F. and a pulse of 110. There was no pigmentation. At autopsy the suprarenal glands were found to be almost completely replaced by caseous masses, and the few remaining cortical cells showed cloudy swelling.—L. G. K.

**(ADRENAL) A case of coexisting suprarenal and renal disease of uncertain origin.** Sparrow (H. G.) and Soden (W. S.), Brit. Med. J. (Lond.), 1919, (ii), 461-462.

The patient, a British soldier in Palestine, was admitted to hospital with weakness, vomiting and night blindness. He appeared very weak and anemic. Blood films were negative for malaria. He had occasional attacks of pyrexia. The blood pressure was low. The urine contained albumin. Some two weeks after admission a blotchy purpuric eruption appeared on the chest, abdomen and extremities. Acetone was then detected in the breath, and the patient vomited a large ascaris worm. The acetone odor then gradually disappeared. The deep reflexes were gradually lost and abnormal skin pigment became evident. There was slight leucocytosis, with a relative increase in polymorphonuclears. The patient was treated with quinine through the greater part of the illness. He died about two months after admission.

The autopsy showed a narrow, atrophied suprarenal cortex and no trace of medullary substance unless represented by some fatty spaces. The kidneys showed a certain amount of degeneration. The intestine showed numerous purpuric patches, with evidence of recent bleeding. No worms were present.—L. G. K.

**ADRENIN, Action of—on the spleen (Milzwirkung des Adrenalins).** Schenk, Deutsche med. Wchnschr. (Berlin), 1919, **45**, 1037.

In cases of haemolytic icterus the author injected adrenalin. Twenty minutes after an injection the enlarged spleen returned temporarily to its normal size. The injection of adrenalin is quite useful to distinguish an enlargened spleen from other tumours (tumours of left adrenals or left kidney).

—J. K.

**(ADRENIN HYPOPHYSIS PANCREAS) Action of organ extracts on induced hyperglycemia (Action des extraits d'organs sur l'hyperglycémie provoquee).** Achard (Ch.), Ribot (A.) and Binet (Leon), C. R. Soc. de Biol. (Paris), 1919, **82,** 788; Abst. Presse Méd. (Paris), 1919, **27,** 401.

The authors produced hyperglycemia in dogs by intravenous injections of glucose. They conclude that the rate and duration of the hyperglycemia depends on the quantity of glucose injected. It is particularly clear in regard to duration. If 0.50 gm. of glucose per kilo. body weight is given, the hyperglycemia lasts 20 minutes; if 1 gm. per kilo. is given, the duration is 40 minutes. Having determined this, they tried the effect of injecting the active principle of various organs.

**Adrenalin.** They first injected 3.5 gm. glucose; two days later, 1 mgm. adrenalin; two days later still, 3.5 gm. glucose plus 1 mgm. adrenalin. The figures show that the addition of adrenalin causes an increase in the blood sugar greater than the sum of the increases obtained with glucose alone or adrenalin alone. The duration of the hyperglycemia was also prolonged, as if under the influence of adrenalin the organism was incapable of fixing or burning the sugar.

**Extract of Hypophysis.** Injection alone causes a slight hyperglycemia. Sugar plus hypophysis increases the hyperglycemia, but not to the same extent as in the case of adrenalin; the rate more than the duration is affected.

**Pancreas.** Commercial extracts alone, or associated with glucose, have no effect. Extracts of fresh pancreas added to the glucose injected causes a diminished hyperglycemia, both in amount and duration.

Added to the glucose-adrenalin mixture, pancreas extract inhibits the action of adrenalin. The same is true when hypophysis is used instead of adrenalin.—T. C. B.

**(ADRENIN) Hemorrhage and adrenalin. Remarks on the vascular reaction to infinitesimal doses (Hémorrhagie et Adrénaline. Remarques sur la réaction vasculaire aux doses infinitésimales).** Bardier (E.), C. R. Soc. de Biol. (Paris), 1919, **82,** 758.

The observations of Rous and Wilson (see Endocrin. 1919, **3,** 188) are confirmed in all points. Hemorrhage causes a diminished pressor response to minute doses of adrenalin. (Does this mean augmentation of the depressor component of the reaction?—Ed.)—T. C. B.

**(ADRENIN) Hemorrhage and adrenalin. Remarks on the cardio-vascular reaction to large doses (Hémorrhagie et**

**adrénalin. Remarques sur la réaction cardio-vasculaire aux fortes doses).** Bardier (E.), C. R. Soc. de Biol. (Paris), 1919, **82**, 760.

In the dog, after bleeding to the extent of 6-7% of the body weight, the pressure being nearly zero, the respiratory movements having nearly disappeared, and with premortal cardiac retardation, it is possible, by injecting 0.03 mgm. of adrenalin per kilo body weight, to observe an energetic cardio-vascular action. This, in strengthening the heart action, favors the resumption of the respiratory rhythm and augments the chances of survival of the animal, if at the same time we give either an artificial serum or transfusion. The conclusion is that the irritability of the cardio-vascular system to large doses of adrenalin in the dog decreases with the magnitude of the hemorrhage, but does not disappear until the "periode ultime." The persistence of this irritability may be of profit in the treatment of hemorrhage.—T. C. B.

**ADRENIN, Arsphenamine and Neoarsphenamine plus—** Beeson (B. B.), Am. J. Syphilis, 1919, **3**, 129.

It is the author's purpose to emphasize the use of adrenalin in the treatment of the "nitroid crisis" and "serous apoplexy" of Milan. The literature is collected which tends to place the etiology of these two conditions largely in an adrenal insufficiency. The evidence upon which this conception rests is: (1) there is a similarity of symptoms in these conditions and in acute adrenal insufficiency, (2) the destructive action of arsenic upon the adrenals has been proven experimentally and repeatedly demonstrated in the autopsy findings of cases dying after salvarsan injections, and (3) adrenalin has therapeutic value in treatment of both these conditions.

The author discusses other factors which may play a part in the production of "nitroid crisis" and "encephalitis hemorrhagica" only to emphasize the importance of adrenal insufficiency, and recommends that 1 mg. adrenin (1 mil of a 1:1000 solution) be given intramuscularly ten minutes before the intravenous injection. As a curative agent, adrenalin will shorten a crisis, but its chief use is as a prophylactic. The author suggests that the best index to the action of adrenalin is the marked pallor which it produces. When this "leuco reaction," as it is termed, is well marked about the site of injection and on the face, it is an indication that the dosage has been sufficient.—J. F.

**(ADRENIN) The action of epinephrine on the cardio-vascular apparatus (L'action de l'adrenaline sur l'appareil cardio-**

**vasculaire).** Binet (L.), Presse. Méd. (Paris), 1917, **25,** 191.

An historical review of the literature of the pharmacodynamic actions of epinephrine on heart, systemic, coronary and pulmonary blood vessels. No original data are presented.—A. L. T.

**ADRENALIN, desiccated THYROID and certain inorganic salts; Effect of, on catalase production.** Burge (W. E.), Am. J. Physiol. (Balt.), 1919, **50,** 165.

The injection of adrenalin into the portal vein stimulates the liver to an increased production of catalase. Assuming that adrenalin is increased during combat, this will explain the increased oxidations. Desiccated thyroid introduced into the alimentary tract also produces an increased output of catalase from the liver. The same is true for large quantities of water, urea, sodium chloride, etc.—T. C. B.

**(ADRENIN) Effect of epinephrin on the electrocardiograms of patients with "irritable heart."** Clough (H. D.), Arch. Int. Med. (Chgo.), 1919, **24,** 284-294.

Patients with "irritable heart" who were sensitive to epinephrin (Goetsch test) gave the following deviations from the normal electrocardiographic records: Changes in conduction (delayed conduction, partial heart block) and the production of ventricular extrasystoles. Other findings were about the same as in normal individuals.—B. T. S.

**(ADRENIN) The changes of blood pressure after injection of adrenalin as a measure of the tonus of the involuntary nervous system (Die Blutdruckveränderung nach Adrenalin injektionen als Gradmesser für den Tonus in autonomen und sympatischen Nervensystem).** Dresel (K.), Deutsche med. Wchnschr. (Berlin), 1919, **45,** 955.

The author injected adrenalin subcutaneously and measured blood pressure every five minutes. Thus he obtained a curve. In normal individuals this curve is a parabola, in vagotonia it has the form of the letter S (in serious cases the blood pressure is first largely diminished). In sympathicotonia the curve rises and falls very steeply.—J. K.

**ADRENALIN in annelids.** Gaskell (J. F.), J. Physiol. (Lond.), 1919, **53,** Proc., xxviii.

Certain annelids, including the Hirudineae, possess nerve cells in their central ganglia which give the chromaffine reac-

tion. These cells reach their highest development in Hirudo medicinalis. G. removed about 400 ganglia, made an extract with Ringer's solution, and tested its activity on the virgin uterus of the cat. A distinct lowering of tone and diminution of rhythm was the result, supporting the view that these nerve cells contain adrenalin. According to G., they are possibly the common ancestors of both the adrenalin secreting tissues of vertebrates and the sympathetic nervous system.—T. C. B.

**(ADRENIN) A simple method for the treatment of chronic bronchitis and bronchial asthma (Een eenvoudig toestelletje ter behandeling van chronische bronchitis en asthma bronchiale).** Haentjens (H. A.), Maandblad voor Specialistische Geneeskunde (Amsterdam), 1919, **2**, 29.

The effects of subcutaneous injections of adrenalin in asthma are well known. The author got still better results when the throat and the larynx were anaestized by alypine and through a catheter in the trachea a mixture of adrenalin and novocain were injected immediately into the lungs.—J. K.

**(ADRENIN) Mode of action of adrenalin against soluble toxins (Du mode d'action de l'adrénaline vis-a-vis des toxines solubles).** Marie (A.), C. R. Soc. de Biol. (Paris), 1919, **82**, 581.

In 1912 Marie showed that adrenalin has a marked power of neutralizing bacterial toxins. In analyzing this action against tetanus toxin, he finds that only its toxicity is neutralized by adrenalin. The antigenic property of the toxin always manifests itself by developing a corresponding antitoxin when the animal is treated with a neutral mixture of toxin-adrenalin. If, instead of the neutral mixture, the adrenalin and tetanus toxin are injected intravenously in separate doses, tetanus does not develop, and even after the separate subcutaneous injection of the two substances the bacterial poison disappears from the blood, whereas in control animals receiving toxin only, the "humeurs" continue to carry appreciable quantities for some time. We know that the alkaloid disappears from the blood in a few minutes; therefore, if in spite of this disappearance of adrenalin, the toxin is no longer discoverable in the blood, some other substance than the adrenalin has neutralized it.—T. C. B.

**(ADRENIN) Surgical shock and some allied conditions.** Medical Research Committee, Brit. M. J. (Lond.), 1917, (i), 381-383.

Dale and Laidlaw studied the effect of intravenous injections of β-iminazolylethylamine (histamine), and found that the profound fall of blood pressure produced by this substance is accompanied by a striking concentration of the blood. The plasma, which normally occupies twice as great a volume as the corpuscles, under these conditions occupies a volume equal to that of the corpuscles, so that one-half of the plasma disappears from the circulation.

Bainbridge and Trevan made similar observations with repeated injections or long-continued infusions of adrenalin. During such injections the portal pressure rises and remains at a high level, while the systemic venous pressure is not significantly altered or else falls slightly. Readings with the hemoglobinometer and the hematocrit show a steady decrease in the volume of the blood plasma relative to that of the corpuscles; this is accompanied by an increase in the viscosity of the blood. When the adrenalin injection is stopped, the arterial pressure rapidly falls to a low level, while the portal pressure remains high, and the animal passes into a condition of shock, with feeble pulse and shallow respiration. This indicates an obstruction of some kind to the flow of blood through the liver (see Endocrin., 1918, **2,** 53), and results in a collection of a large part of the blood in the splanchnic area. When this is added to the steady loss of fluid by exudation into the tissues, the output of the heart fails from defective venous inflow and a profound collapse of arterial pressure results. The increased viscosity further retards the flow. Consequently the oxygen supply to the tissues becomes inadequate.

From the above facts it is evident that adrenalin should not be used in the treatment of shock, since it is likely to aggravate the condition. Pituitrin, however, is recommended.—L. G. K.

**(ADRENIN) The influence of chemical substances on the action of adrenalin (Incompatibilita chimiche dell' adrenalina).** Piccinini (P.), Gazzetta degli Ospedali (Milano), 1919, **40,** 336.

Valeri has shown that the influence of adrenalin on the eye and on the blood pressure disappears when the adrenalin is combined with iron or arsenic compound. Piccinini controlled these experiments with lactate, citrate and phosphate of iron and with arsenate of sodium and confirmed the results of Valeri. If he used, however, instead of adrenalin, an extract of the whole adrenal gland, these chemical substances had no

influence on the biological action of the extract on the eye of the frog or the blood pressure in dogs.—J. K.

**(ADRENIN PANCREAS) The supposed antagonism between internal pancreatic secretion and adrenaline on smooth muscular fibres of vessels.** Polettini (B. D.), Atti ist. Veneto, 1916, **16**, 503-508.

Surviving vessels, in Ringer's solution, modified specially after Meyer and Müller for these tissues, were treated with (1) an adrenaline-pancreatic solution, the two being left in contact for 48 hours; (2) Ringer's solution and adrenaline. Graphs show no appreciable difference in the two cases. Vessels and adrenaline from cattle were used.—Physiol. Abst., **4**, 340.

**ADRENIN, Influence of—and physostigmine upon the blood picture in malaria.** Pulay (E.), Ztschr. f. exp. Med., 1917, **7**, 108-118.

Adrenaline causes an increase in the relative lymphocytosis but still below the normal; physostigmine causes a decrease. Both produce an increase in the polymorphonuclear leucocytes. —Chem. Abst., **13**, 2925.

**ADRENALIN in blackwater fever.** Robertson (J. A.), Brit. Med. J. (Lond.), 1919, (ii), 272.

Adrenalin chloride is given in a dose of 20 minims every four hours. After the first three or four doses the urine clears up remarkably. No quinine is given. Iron tonics without quinine are prescribed during convalescence. The author suggests that the adrenalin balances a suprarenal insufficiency, which is perhaps the cause of the hemoglobinuria in some cases of malarial infection. No evidence is submitted that such is the case.—L. G. K.

**(ADRENIN) Neglect of the internal secretions as a cause of high mortality in many diseases.** Sajous (C. E. de M.), J. Med. Soc. New Jersey (Orange), 1918, **15**, 109-116.

The author holds that the persistent high mortality of many diseases is due to the fact that the physio-pathological role of the ductless glands in these diseases is virtually disregarded. He cites among other diseases the mortality of which has not been reduced by modern knowledge, pneumonia, characterized by Osler: "Almost the natural death of old people,"

in which death sometimes occurs unexpectedly, in the midst of the patient's daily occupation. Sajous does not regard this senile form—the cause of a large proportion of the deaths attributed to the disease—as a true pneumonia, but as the result of a more or less sudden failure of the adrenals. The symptoms in most of these cases, in fact, include but few of those peculiar to pneumonia: the fever is slight, there is a moderate rise of blood pressure, but little if any cough or expectoration, no pain in the chest, soon followed by rapid lowering of the arterial tension, marked lividity, pulmonary edema and extreme asthenia—all typical signs of adrenal failure. A suggestive fact in this connection is that dilatation of the right heart sometimes precedes infection, thus indicatng that the latter is secondary to the adrenal failure. An illustration shows the steady loss of vascularity of the adrenals as age advances, a condition which leads these to fail readily under varying degrees of stress in the aged, primarily in some cases or a slight pneumococcic infection due to exposure, fatigue, etc., in others. Sajous states many of these cases would be saved were the role of the adrenals in the process recognized and the patient carried safely through the stage of acute adrenal failure. Injections of 10 minim doses of epinephrin 1:1000 solution in a syringeful of saline solution, are administered slowly, avoiding a vein, every two hours, three times, then, when the cardiac action improves sufficiently, four times daily. Antistreptococcus serum is indicated, rather than vaccines, the latter serving only to excite adrenals that are unable to respond, while the serum contributes to the systemic asset in antibodies. Sustaining food in small quantities, creosote carbonate to prevent tympanites and avoidance of depressants, particularly the opiates and coal tars, are important therapeutic aids.

Another phase of adrenal failure connected with infections which the author has termed "terminal hypoadrenia" may occur at all ages. As its name suggests, this condition occurs late in the history of the disease, owing mainly to exhaustion of the adrenals during an exceptionally severe and prolonged febrile process. Hence its frequent occurrence in typhoid fever, broncho-pneumonia, diphtheria, scarlatina, erysipelas, septicemia, mumps, severe measles and peritonitis. The signs differ but little from those observed in senile pneumonia, and if the failure of the adrenals is overlooked in these cases, death often occurs from exhaustion, notwithstanding the so-called "supporting" treatment. Conversely, the use of epinephrin as above described, in addition to these measures, often turns the tide with surprising promptness.—Author's Abst.

**ADRENIN, The action of—on the muscular coat of digestive organs.** Spadolini (I.), Arch. di Fisiol. (Firenze), 1918, **16,** 135-150.

Both adrenalin and sympathetic nerve fibres may provoke inhibitory as well as motor reactions on the part of the muscular coat of the stomach and small intestine. These antagonistic reactions are in relation with the quantity of adrenalin injected into the blood-stream; the inhibition is provoked by solutions more dilute than those necessary to produce motor phenomena. These results are explained by Spadolini having recourse to Langley's doctrine of receptive substances. Small quantities of adrenalin would become bound by the inhibitory receptive substances, whereas larger quantities could combine also with the motor ones; inhibitory receptors would have a greater affinity for adrenalin than the motor ones, which could combine with adrenalin only after the inhibitory receptors have been fully bound by it. For that, of course, both inhibitory and motor receptors must be present in the same sets of cells.—Physiol. Abst., **4,** 340.

**(ADRENIN) The effects of epinephrin on the basal metabolism in soldiers with "irritable heart," in hyperthyroidism and in normal men.** Tompkins (Edna H.), Sturgies (C. C.) and Wearn (J. T.), Arch. Int. Med. (Chgo.), 1919, **24,** 269-283.

The same technique was employed as in the preceding experiments.

Conclusions: Intramuscular injections of epinephrin cause an increase of total metabolism in normal men and patients with "irritable heart" and in hyperthyroidism. Increase in metabolism is greater in cases showing a positive "Goetsch" reaction to epinephrin. The increase in metabolism is due to some other factor than excitement or stimulation of heart by the injection of epinephrin; it may be due to increased muscular tonus or hyperglycemia.—B. T. S.

**ADRENIN treatment of serious lung diseases in infants (Adrenalinbehandlung schwerer Lungenerkrankungen bei Säuglingen).** Vogel, Wiener klin. Wchnschr., 1919, **32,** 850; Berl. klin. Wchnschr., 1919, **56,** 503.

The author saw good results from subcutaneous injections of 2-5 cc. of adrenalin (1:1000 solution) in serious capillary bronchitis and bronchopneumonia of infants.—J. K.

**(ADRENIN) Effects of the injection of epinephrin in soldiers with "irritable heart."** Wearn (J. T.) and Sturgis (C. C.), Arch. Int. Med. (Chgo.), 1919, **24**, 247-268.

Studies were begun to determine the relation of the thyroid gland to the symptom complex of "irritable heart of soldiers." From this study it was concluded that hyperthyroidism does not play a significant role in the condition. In these studies of the basal metabolism it was decided to employ at the same time the "Goetsch" epinephrin test. It was soon observed that some cases with normal basal metabolism showed definite hypersensitiveness to epinephrin.

Studies were made on both normal soldiers and soldiers with irritable hearts, who had been in training for a number of months. The technic was the same as that followed by Goetsch. After an hour's absolute rest in bed, control readings of blood pressure, pulse and respiratory rates are made; also a note is made of objective symptoms. After satisfactory control readings are made, 0.5 cc. 1:1000 solution of freshly prepared epinephrin is injected deep into the deltoid muscle. Readings as above are made at five minute intervals for one hour. A positive reaction manifests itself in about twelve minutes as a rise in systolic blood pressure, increased pulse rate, tremor, precordial pain, nervousness, etc.

The results of the studies were as follows: Of twenty-six normal soldiers (controls) who had had severe army training for fourteen months, not one gave a positive reaction; of seventy-three patients with symptoms of "irritable heart" sixty per cent gave a reaction which definitely indicated a hypersensitiveness to epinephrin.—B. T. S.

**(AUTONOMIC N. S.) Treatment of vagotony and sympathetic-cotony.** Noronha (H.), Arch. Brasil. de Med. (Rio de Janeiro), 1919, **9**, 92-100.

Noronha warns that the main thing in treatment of either condition is to aim to restore tone to the unstable nervous system as a whole; atropin can then be given for vagotony and epinephrin for sympatheticotony, but the doses should be small and cautiously given.—J. Am. M. Ass., **73**, 650.

**(BLOOD SUGAR ADRENIN DIABETES) Permeability of erythrocytes to sugars in hyperglycemia.** Kozawa (S.), Tokyo Igak. Zasshi, 1916, **30**, 9-18; Jap. Med. Lit., 1917, **2**, 2.

In vitro the hexoses and the pentoses readily penetrate the erythrocytes of man and the monkey, and penetrate those of the

dog to a certain extent, but do not at all penetrate those of the puppy, goat, pig, cat, or cattle. In a diabetic patient the sugar content of the corpuscles was definitely increased, and approached, but never exceeded, that of the serum; the cells were swollen; and the hematocrit reading was twice the normal value for the same number of cells. Adrenaline hyperglycemia in puppies did not alter the sugar content of the red cells; in dogs it produced a definite increase in the sugar content of these cells, though not to such a degree as occurred in the experiments in vitro.—Physiol. Abst., **3**, 504.

**Cataract and INTERNAL SECRETION.** Schioetz (C.), Norsk mag. f. laegevid. (Christiania), 1913, nr. 9.

Cataracta centralis congenita is fairly frequent in cretinous calves, which has first been demonstrated by the Norwegian veterinary surgeon Loeken. This fact brings the author to discuss the occurrence of cataract in various endocrine disorders. Cataract is observed after extirpation of the parathyroids and diabetic cataract may possibly be referred to the pancreas; Langfeldt (Norway) has seen cataract in dogs after pancreatectomy. Senile cataract is hypothetically referred to hypofunction of the sexual glands. Cataract is further discussed in relation to diseases of the thyroid, pituitary and suprarenals.

—K. M.

**(CORPUS LUTEUM) Double ovariectomy because of bilateral ovarian cysts, at the end of the fourth month of pregnancy. Suppression of the corpus luteum. Delivery at term. (Ovariotomie double pour kyste ovariques bilateraux, a la fin du quatrième mois dela grossesse. Suppression du corps jaune. Accouchement terme).** Grosse (A.), Ann. de Gyn. et d'Obst. (Paris), 1919, **13**, 464-473.

A report of a case of bilateral ovarian cysts necessitating removal by laparotomy in the fourth month of pregnancy, followed by delivery after a normal and uneventful course. The milk secretion was marked and the child breast fed. References are given to the literature of similar cases from which, and in consideration of his own results, the author concludes that it does not appear as if the corpus luteum is indispensible for embryonic and foetal development at the beginning of pregnancy and that its suppression is not sure to cause abortion.—F. S. H.

**CORPUS LUTEUM, The use of—in pregnancy.** Welz (W. E.), J. Michigan State M. Soc. (Grand Rapids), 1919, **18**, 373-376.

The toxemia of early pregnancy is equivalent to corpus luteum deficiency. Extracts of the corpus luteum relieve such symptoms and may control habitual abortion. The latter is considered the result of deficient corpus luteum development in early pregnancy.—H. W.

**(CORPUS LUTEUM) Corpus luteum extracts in the vomiting of pregnancy, with report of cases.** Quigley (J. K.), Am. J. Obst. (N. Y.), 1919, **80**, 183-185.

Of seventeen cases of vomiting of pregnancy, twelve were benefited permanently by the use of corpus luteum extracts, four were benefited but relapsed, and one was a complete failure.—H. W.

**DIABETES innocens.** Solomon (H.), Wiener klin Wchnschr. 1919, **32**, 871.

An important artiele. The author saw cases of diabetes innocens during five years, not becoming more serious. The blood sugar is on the empty stomach mostly normal; in a few cases it was slightly increased. There are cases who have a carbohydrate tolerance, but in other cases, even after the smallest amount of ingested carbohydrates, a trace of sugar comes in urine. If more carbohydrates are given the amount of sugar in the urine is not increased. In rare cases larger amounts of sugar are excreted (up to 40 grams) daily. In these cases blood sugar estimations are necessary to distinguish them from ordinary diabetes.—J. K.

**DIABETES and complication with surgical diseases (Glykosurie und Diabetes bei chirurgischen Erkrankungen).** Weiland (W.), Berl. klin. Wchnschr., 1919, **56**, 887; same artiele but more detailed, in Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1919, **31**, 473.

Traumatic diabetes is very rare; the author has seen only one case. Traumatic glycosuria is, however, very frequent. Surgical diseases caused by diabetes do not exist. The gangrene as it is frequently seen in diabetes is of arteriosclerotic origin.—J. K.

**DUCTLESS GLANDS in military practice.** Sajous (C. E. de M.), Penn. Med. J. (Athens), 1919, **22,** 215-220; N. Y. M. J., 1919, **109,** 569.

The author calls attention to the large number of hyperthyroid soldiers detected in army practice. The asthenia of excessive strain, the sudden deaths of adrenal failure, the soldier's irritable heart, warfare shock, the terminal hypoadrenia of infections, the collapse following antityphoid vaccination are examples of disorders in which the adrenals take a prominent part, and in which appropriate therapy can accomplish considerable good, and even save life. Sajous ventures the belief that the irritable heart of the soldier is frequently due to exhaustion of the adrenals, while in others an overactive thyroid is responsible. In the latter group adrenalin, nitrites and digitalis are ineffective and prolonged mental, physical and emotional rest are necessary for recovery.—H. L.

**DYSTROPHIA musculorum progressiva.** Schmidjell (F.), Wiener klin. Wchnschr., 1919, **32,** 867.

Of no direct endocrine interest.—J. K.

**ENDOCRINE DISEASE, Progressive muscular dystrophy as an—.** Timme (W.), Arch. Int. Med. (Chgo.), 1917, **19,** 79-104.

Exhaustive search of the literature, by the writer, impressed him with the fact that accompanying the muscular dystrophies, endocrine disturbances of one form or another were present. He reports a somewhat atypical form of muscular dystrophy resembling the familial infantile form. This disease occurred in four generations. Four out of five individuals having this condition, showed distinct changes in the region of the pineal gland. Three of the four patients were under twenty-four years of age.—J. H. L.

**(ENDOCRINE EXTRACTS) Treatment of shock by complex artificial serum (A propos du traitement du shock. Essais d'un sérum artificial complexe).** Descomps and Clermonthe, Bull. Soc. de Chir. (Paris), 1918,—,—, (July 18).

The "serum" referred to is a modified Ringer-Locke solution plus strychnine, digitalin and extracts of endocrine organs (thyroid, spleen, pituitary, adrenal and testis).—Physiol. Abst., **4,** 346.

**ENDOCRINE GLANDS, Affections of—in acquired syphilis.** Hazen (H. H.), Am. J. Syphilis, 1919, **3**, 205.

This paper does not lend itself readily to abstracting inasmuch as it is a resumé of the literature. Syphilis is discussed in its relation to hyperthyroidism and hypothyroidism. Emphasis is placed upon the suggestion of Mendel that many of the so-called cases of thyroid syphilis might be merely examples of iodine thyroiditis. The literature of syphilis of the parathyroids, thymus, pineal gland, adrenals, and pituitary is treated.

—J. F.

**(ENDOCRINE GLANDS) The climacteric of life.** Rankin (G.), Brit. Med. J. (Lond.), 1919, (i), 63-67.

The author claims that for men as well as for women there is a climacteric period, which coincides with life's full maturity. It occurs from seven to ten years later in men than in women, and in both is a time of special liability to the development of disease, especially of such as may be regarded as the expression of hereditary tendencies that have down to this period remained dormant. The immediate counterpart in man of the ovarian changes in woman is to be found in the structural alterations which become established in the prostate gland. Acute illnesses occurring during this period are attended with more than average risk, and the frequency of malignant growths at this age is well known. Besides these conditions arteriosclerosis, interstitial nephritis and diabetes are common ailments in men between 55 and 63, while in women colitis, rheumatoid arthritis and hyperthyroidism are common accompaniments of the change of life.

The author claims that at this age the starvation treatment for diabetes is such a tax upon the nervous control of the patient that it imperils his "serenity of temper and happiness of life." And besides, the author minimizes the importance of sugar in the urine of elderly men, claiming that it does not interfere with their life or work to an appreciable extent.

—L. G. K.

**ENDOCRINE influence of the pylorus.** Frumson (L. G.), Med. Fortnight. (St. Louis), 1919, **51**, 157-158.

A most facetious attack upon all known facts and theories relative to gastrointestinal disturbances and upon investigators generally. However, Frumson claims for himself great results in the treatment of achylia by the administration of watery extracts of the pylorus of cattle.—H. W.

**ENDOCRINE manifestations.** Strauss (S. G.), U. S. Nav. Med. Bull. (Washington, D. C.), 1918, **12**, 609-615.

An appeal for the study of subjective as well as objective symptoms and for a consideration of the patient as a whole, instead of the complainant part alone. The article is accompanied by a description of two cases presenting no laboratory proofs of adrenal derangement but which, being studied from a general knowledge of the possibilities of such disorder and treated accordingly, gave favorable response and substantiated the value of the method advocated.—F. S. H.

**(ENDOCRINE ORGANS) Cerebral localization from the point of view of biologic psychology (Las localizaciones cerebrales bajo el punto de vista de la Psicología Biológica).** Enrique Mouchet, Prensa Med. Argentina, 1919,—,—, (No. 2.)

The totality of intelligence is derived not through the senses alone. The cerebrum receives an inner stimulus through the blood as well as internal secretions proper which contribute to the formation of instincts and, to a notable extent, of the psychic qualities.—B. A. H.

**(ENDOCRINE ORGANS) The differentiation of mankind into racial types.** Gallwey (T. J.), Lancet (Lond.), 1919, (ii), 666.

Gallwey criticises the view of Keith (see abstract in this issue) that the differentiation of the races of mankind has been due to varying degrees of endocrine activity. He claims that environment alone is responsible for the various types, although he does not show why environment could not modify the type through modifications in the ductless glandular system .

—L. G. K.

**(ENDOCRINE ORGANS) Dystrophie myotonica.** Kastan, Berl. klin. Wchnschr., 1919, **56**, 837.

A case of dystrophia myotonica (myotonia atrophica). The thyroid was only half the size of a normal organ; both testicles were atrophic. The X-rays showed no changes in the hypophysis.—J. K.

**(ENDOCRINE ORGANS) The differentiation of mankind into racial types.** Keith (A.), Lancet (Lond.), 1919, (ii), 553-556.

This paper has attracted a good deal of attention in the lay press as evidenced by the number of newspaper articles which have lately appeared on this subject. The author sets

forth the view that the distinguishing characteristics of the races of mankind have been produced by the varying degrees of activity manifested by the ductless glands in the different races. For instance, he explains the sharp and pronounced nasalisation of the face, the tendency to strong eyebrow ridges, the prominent chin, the tendency to bulk of body and height of stature in Europeans as a result of a greater activity of the pituitary gland in them than in the Negro or Mongol races. Similarly the beardless face and almost hairless body of the Negro and Mongol are attributed to a lesser degree of activity on the part of the interstitial cells of the gonads. The suprarenals, because of the darkening of the skin in Addison's disease, are said to regulate the amount of pigmentation of the skin. A reduced activity of the thyroid is supposed to account for the characteristic aspect of the Mongolian face. The hypothesis thus attributes to the Caucasian a slight degree of acromegaly while it declares that the salient characteristics of the Mongolian and Negro races are due to a tendency toward eunuchism, Addison's disease and cretinism. Achondroplastic dwarfs and Mongoloid idiots are regarded as the results of defects in the growth regulating mechanism of the thyroid, and since, in the opinion of the author, both these types resemble the Mongolian, this is advanced as an added piece of evidence that hypothyroidism has been partly responsible for the Mongolian type of man.

(The hypothesis is unsupported by experimental evidence, and the author has apparently taken advantage of the unsettled condition of our knowledge of the ductless glands to put forth a theory which explains the unsolved in terms of the unknown.)—L. G. K.

**(ENDOCRINE ORGANS) Endocrine glands and fever. (Glandes endocrines et fiévre).** Leopold-Levi, C. R. Soc. Biol. (Paris), 1919, **82**, 410-412.

The author is of the opinion that endocrine activity and the production of fever are very closely related. He believes that the thyroid, ovary, suprarenal and anterior lobe of the pituitary can all produce fever or increase the fever of autoinfection, the premenstrual period and particularly the fever of tuberculosis.—L. G. K.

**(ENDOCRINE ORGANS) Bradykardie mit Hypotonie.** Lommel, Deutsche med. Wchnschr. (Berlin), 1919, **45**, 1096.

The author observed many cases of slow action of the heart combined with a low blood pressure. Often the temper-

ature was low, there were oedemas and eosinophilia. Perhaps an abnormal function of the endocrine organs plays a part in the disease, but treatment with adrenalin, with thyroidin, with pituglandol and with extract of gonads had no effect whatever.—J. K.

**ENDOCRINE organs, Diseases of the—.** Poulten (E. P.), Guy's Hosp. Gaz. (Lond.), 1918, **32,** 234-241.

This is an abstract of two clinical lectures by the author and contains but a brief survey of the outstanding features of the clinical significance of adrenal, pituitary, thyroid and parathyroid syndromes.—F. S. H.

**(ENDOCRINE ORGANS) Changes in the weights of the various parts, systems and organs in albino rats kept at birth weight by underfeeding for various periods.** Stewart (C. A.), Am. J. Physiol. (Balt.), 1919, **48,** 67-78.

The weights of the various organs, systems and parts of the body were studied in eight newborn controls and 15 test rats kept at birth weight by underfeeding for period ending at 11 to 22 days of age. In the test animals the individual endocrine glands showed the following percentage increase in weights when compared to the corresponding organs of newborn rats: Testes 374, spleen 33, hypophysis 29, pineal gland 21. The thyroid, ovaries and suprarenals showed practically no change, while the thymus decreased in weight 49 per cent.—L. G. K.

**(ENDOCRINE ORGANS) Diet in chronic arthritis.** Thomson (F. G.), Practitioner (Lond.), 1919, **103,** 10-121.

In discussing the importance of vitamines in feeding cases of chronic arthritis the author states that lack of these food constituents results in ill-balanced function of the endocrine glands, which he considers a constant feature of arthritis. "Whereas in rheumatoid arthritis, hyperthyroidism due to toxic thyroiditis occurs with great frequency, in osteo-arthritis, fibrositis, and chronic gout, the balance swings in the other direction, with thyroid inertia and hyperactivity of the suprarenal system. — — — — Modern investigation has shown that uncooked food is an essential element in diet, owing to the action of vitamines in promoting normal digestive and assimilative processes and maintaining the balance of endocrine activity."—H. L.

**ENDOCRINOPATHIES, Clinical manifestations and basis for treatment of some—.** Timme (W.), J. Nerv. and Ment. Dis. (N. Y.), 1918, **47,** 446-449.

Timme points out the inadequacy of some of the present-day endocrine terminology in that such names as exophthalmic goitre do not cover the entire or even the fundamental pathology. He distinguishes between the abnormal glandular manifestations which dominate the clinical picture and the disturbed gland which is the key to the whole syndrome. The two are not always identical and certainly difficult to determine because of such complicated inter-relations between the various glands. The problem then lies in selecting the crucial symptom or the crucial gland on which to base the therapy.—A. R. T.

**(GONADS) A case of hypernephroma (Ein Fall von Hypernephrom).** Bittorf, Deutsche med. Wchnschr. (Berlin), 1919, **45,** 981.

A very short description of a man with hypernephroma, atrophy of the testes and development of female breasts.
—J. K.

**(GONADS) Steinach's treatment of homosexuality (De behandeling van homosexualiteit volgens Steinach).** de Boer (S.), Geneeskundige Bladen (Haarlem), 1919, **21,** 175.

Gives a very good review on the work of Steinach and the literature on this point. No new facts.—J. K.

**(GONADS) Masculine tubular hermaphrodism. Abdominal hysterectomy in the course of a radical cure for inguinal hernia in a man of 31 (Hermaphrodism tubulaire masculin. Hysterectomie abdominable au cours d' une cure radicale de hernie inguinale chez un homme de 31 ans).** Couvelaire (A.) and Duclaux (H.), Ann. de. Gyn. et d'Obst. (Paris), 1919, **13,** 474-478.

An interesting case of masculine tubular hermaphrodism of the internal variety consisting in the heterologous development of the Müllerian ducts to a normal degree, in contradistinction to the usual condition observed in the female organs when found in the male, which are usually rudimentary in character. The external appearance was thoroughly masculine without any secondary sexual characteristics of the female. He was married and his wife had given birth to two children since that time. The testicle that was removed contained spermatazoa as did his semen on ejaculation. On operation for in-

guinal hernia, scrotal variety, there was discovered in the scrotum a well developed uterus 10 cm. in length and 4 cm. in breadth at its maximum.—F. S. H.

**GONADS, Structure of—. (Bauplan der Keimdrüsen).** Kohn (A.), Wiener klin Wchnschr. (Vienna), 1919, **32,** 50; Berliner klin. Wchnschr., 1919, **56,** 70.

A general review.—J. K.

**(GONADS) Influence of the interstitial gland upon body temperature (Über die Abhängigkeit der Körpertemperatur von der Pubertätsdrüse).** Lipschütz (A.), Arch. f. d. ges. Physiol. (Bonn), 1917, **168,** 177.

The rectal temperatures of normal male and female, of castrated male and female guinea pigs without grafts and of castrated male and female guinea pigs into which ovaries and testes, respectively, had been grafted, were measured. Result: The interstitial gland of the male sex gland has no influence upon the body temperature of the male and probably no influence upon the temperature of the castrated female when it is grafted into the latter. The interstitial gland of the female gonad increases the temperature from 0.4 to 0.5° C., as indicated by the fact that in castrated females the body temperature is 0.4° C. lower than in normal females, while in castrated males into which ovaries were grafted, it is 0.5° C. higher than in castrated males into which no ovaries had been grafted.

—E. U.

**GONADS, The formation of sexual characters by the—. (Die Gestaltung der Geschlechsmerkmale durch die Pubertätsdrüsen).** Lipschütz (A.), Arch. f. Entw. (Berlin), 1918, **44,** 396.

A review of the work on the influence of the removal and transplantation of the gonads on sexual characters. No new data.—M. M. H.

**(GONADS) Transformation of the clitoris into a penis-like organ through experimental masculinization. (Umwandlung der Clitoris in ein penisartiges Organ bei der experimentellen Maskulierung.)** Lipschütz (A.), Arch. f. Entw. (Berlin), 1918, **44,** 198.

After implantation of a testis in a spayed female guinea pig, the clitoris develops into an organ somewhat like the penis of a normal male. The foreskin and the corpora cavernosa

penis are well developed, and "piercing" organs are present, though abnormally placed. The organ is shorter than a normal penis and the growth of the corpus cavernosum urethrae is not stimulated by the operation.—M. M. H.

**GONADS, Fundamentals of knowledge about the—. (Prinzipielles zur Lehre von der Pubertätsdrüse).** Lipschütz (A.), Arch. f. Entw. (Berlin), 1918, **44**, 207.

Further discussion of the reasons why different parts of an organ (e. g. the clitoris) react differently to transplantation of the gonads. No new data.—M. M. H.

**(GONADS) Die spermatogenesis des Grottenolmes.** Stieve (H.), Anat. Anz. (Jena), 1918, **51**, 321.

A cytological study of the germ cells of the amphibian Proteus anguineus. Not of endocrine interest.—E. R. H.

**(GONADS) Hermaphroditism in men (Ueber Zwitterbildung bein Menschen).** Polano. Deutsche med. Wchnschr. (Berlin), 1919, **45**, 1231.

Report of a remarkable case. The clitoris was developed like a penis, but the urethra ended at the base of the organ. By an operation the end of the urethra was transplanted to the glans. When the patient was 18, she menstruated regularly from this artificial orifice. The secondary sexual characteristics were mixed, but more female than male. At operation for an abdominal tumor a normal uterus was found. In one of the ovaries normal testicular tissue was seen. To this ovary was attached a vas deferens with a normal epididymis. —J. K.

**(GONADS) Männlicher Pseudohermaphroditismus.** Schmalfuss. Berl. klin. Wchnschr., 1919, **56**, 789.

A girl with female external genitals underwent a "herniotomy." One normal and one atrophic testicle were found. Six months later the patient died of sepsis. Though during the operation two testicles were removed, at the postmortem examination living spermatozoa were found in the vesiculi seminalis.—J. K.

**(HORMONES) An hypothesis of "hormone hunger."** Harrower (Henry R.), Med. Rec. (N. Y.), 1919, **96**, 276-278.

Harrower notes that in his experience with organotherapy

brilliant results are obtained in some cases of endocrine disturbance and no results whatever in clinically similar cases. This has led him to formulate "an hypothesis of hormone hunger." He believes that each organ in the body has a selective capacity to pick up and utilize certain hormones that are circulating in the blood stream, and that the more urgent its requirement for a specific hormone, the more "hungry" it is, the more readily it picks up and utilizes this hormone. The interrelationship of the ductless glands, with the result that abnormal secretion of one produces alterations in the activity of the others, justifies pluriglandular therapy, in Harrower's opinion, and removes from it the odium of "shotgun" therapy. In giving pluriglandular products, Harrower thinks the opportunity is given the body to do its own selecting. "We can trust the organism to pick out from the menu we offer it those hormones that it needs most, and, too, in the degree it needs them." (If this hypothesis be true, why should patients with the same clinical signs and symptoms, and therefore the same "hormone hunger," respond differently to the same ductless gland diet? The author has not proved his point, and the encouragement of unintelligent, indiscriminate pluriglandular therapy, usually in totally inadequate dosage, is most unwise; Osler has recently given a timely warning and deserved criticism of this latest therapeutic "fad.")—H. L.

**HORMONES and phosphatides.** Fraenkel (S.) and Herrmann (E.), U. S. Patent No. 1,314,321, Aug. 26, 1919.

A preparation suitable for treatment of disorders produced by failure of the ovarian functions is prepared in the following manner: 50 pieces of human placenta are carefully dried in vacuo and pulverized and the resulting material, about 5000 g. of dry substance, is extracted with ether. After evaporation of the ether, the phosphatides are precipitated from the residue by adding a 4-fold amount of acetone. The acetone-containing mother liquid is freed from solvent in vacuo. The residue is then taken up in cold alcohol, by which treatment a great part of cholesterol and cholesterol esters (less soluble in the cold solvents) is separated out. After evaporation of the alcohol, the residue is purified by fractional distillation in the highest vacuum possible. Under a pressure of 0.06 mm. Hg a mixture of hormones with cholesterol distils over as the principal fraction. By treating this distillate with cold alcohol, the hormones are dissolved, while cholesterol and saturated esters of cholesterol crystallize out. For a further purification of the desired product, a second fractionation in a high vacuum can

be utilized after evaporation of the alcohol. The product is a thickly flowing oily liquid showing the typical reactions of cholesterol. Various modifications of the procedure are described.—Chem. Abst. **13,** 2736.

**HORMONES, Hypothesis concerning—. (Hypothèse sur les hormones).** Ide, C. R. Soc. de Biol. (Paris), 1919, **82,** 944.

The role of the "glandes sanguines" can be explained by their embryologic origin. They produce substances useful to themselves and to their sister cells. This hypothesis is suggested by a number of facts.

Adrenalin is a specific excitant of the dorso-lumbar sympathetic. Embryologically, there are two elements in the suprarenals, nervous ganglia coming from the dorsal region of the cord and going to meet the coelomic islets. These two elements intermingle and unite intimately, the nervous part forming the medulla of the suprarenals. These chromophile cells are nervous cells that have become secretory, and their secretion is a special excitant to their group. They work for their cell-sisters. The other glands are considered from the same point of view.

If we some day find a "vagotonin" analogous to adrenalin, but exciting the terminations of the vagus or parasympathetic, it will spring from a parasympathetic nervous element originating in the cervical or cranial portion of the medullary canal. It is useless to look for it in the lymphatics or the marrow of the bones. It will be necessary to look for it in the head about the pharynx, or at the surface of the midbrain.—T. C. B.

**(HYPOPHYSIS) Hypophysaire Polydipsie.** Arnstein (A.), Wiener klin. Wchnschr., 1919, **32,** 928.

The author demonstrated a woman of 47 with polydipsia. Four years before a stomach cancer had been removed. Perhaps the polydipsia was due to a metastasis of the first tumor into the hypophysis. Injections of pituglandol was followed by improvement.—J. K.

**(HYPOPHYSIS) Hypophysispolydipsie und—polyurie.** Arnstein (A.), Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1176.

A woman of 47, three years after an amputation of a breast for cancer, developed diuresis of 5 liters daily. The urine had a specific gravity of 1003-1007. She drank over 5 liters of water in 24 hours. Injection of pituglandol diminished

the quantity of urine to about 2 liters. The quantity of ingested water diminished also in the same proportion.—J. K.

**HYPOPHYSIS, Tumor of the—(Hypophysisgezwel).** Beukers (A. C. M.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1919, **63** (II), 1312.

A patient had adiposity but no polyuria of acromegaly. There were also present bilateral atrophy of the optic nerve and headaches. The roentgenogram disclosed no abnormality. Other endocrine organs than the hypophysis were apparently normal. At operation a hypophyseal tumor was removed. The microscopic diagnosis was cancer. After the operation the patient saw much better, but her adiposity increased. The headaches disappeared and the psyche was much improved.—J. K.

**(HYPOPHYSIS) Posterior pituitary secretion in the treatment of mitral regurgitation.** Bate (R. A.), Ky. Med. J. (Bowling Green), 1919, **17**, 419-422.

Cases of "rheumatic" endocarditis may be supported to compensation by posterior pituitary extracts.—H. W.

**(HYPOPHYSIS) The infundibular syndrome in a case of tumor of the third ventricle (Le syndrome infundibulaire dans un cas de tumeur du troisième ventricule).** Claude (H.) and Lhermitte (J.), Presse méd. (Paris), 1917, **25**, 417.

The well-known syndrome consisting of narcoleptic attacks, of cardiovascular irregularities (tachycardia, irregularity of the pulse, extra-systoles, embryocardia and increased blood pressure) and polyuria with polydipsia are not, as it is frequently claimed, due to lesions of the hypophysis, but to lesions of the infundibulum. The authors had occasion to observe a patient in whom, at autopsy, a tumor of the third ventricle was found. Examination revealed an epithelial cystic tumor formed from the ventral wall of the third ventricle and distinctly confined to the infundibulum; the hypophysis, however, was completely normal. This patient had shown the following symptoms: Bitemporal hemianopsia, attacks of dysarthria, amnesia and delirium, attacks of narcolepsy, tachycardia, irregularity of the heart beat, extra systoles, embryocardia and increased blood pressure, polyuria and polydipsia. The first two symptoms proved to be due to pressure exerted by the tumor upon the optic region and upon the pedunculi cerebrales, respectively. The disturbances of the mental condition are not due to the lesions of any specific region of the

brain, since they are caused very frequently by all sorts of brain tumors; it may be that they are the result of circulatory disturbances caused by these tumors.

In contradiction to A. Salmon's hypothesis of a hypophyseal origin of narcoleptic attacks, the case in question demonstrates that a disturbance of the excretory function of the pituitary gland is not the cause of this phenomenon, since the hypophysis was entirely normal. The same is true for the cardio-vascular disturbances, and in this respect clinical experience fully confirms the experimental results obtained by several observers, and particularly by Aschner, which show that it is the excitation of the tuber cinereum and the infundibulum, and not of the hypophysis, which produce the phenomena in question. Finally the experimental data obtained by J. Camus and G. Roussy proving that experimental lesions of the tuber cinereum and infundibulum cause polyuria seem to be well in accordance with the clinical data observed here; polyuria accompanied by polydipsia is due to lesions of the basis of the third ventricle, but not to lesions of the hypophysis. The most important result of this clinical observation seems to be that the secretion of the pituitary gland does not play any role in the cardio-vascular phenomena in question, nor in the regulation of the metabolic processes of water excretion.

—E. U.

**(HYPOPHYSIS) Pituitary treatment in gynecology.** Dalché (P.), Rev. Mens. de Gynéc. et d'Obstét. (Paris), 1919, **14**, 165-182.

Dalché gives pituitary by the mouth, preferring the dry extract of the whole gland, giving from two to four cachets a day of 0.10 gm. each. This treatment can be applied in every case of metrorrhagia, and it often will give good results. But success depends on its being kept up perseveringly for weeks and months with bleeding fibromas, diffuse fibromatosis and sclerosis of the uterus, retrodisplacement with congestion, virginal metrorrhagia, intermenstrual dysmenorrhea—whenever, in short, the aim is to modify a condition of long standing. For example, a young girl with too frequent and too profuse menstruation should take the pituitary extract every day for a month, then for two weeks each month, beginning the week before the anticipated menses and continuing till the close. The other two weeks he orders 10 drops of tincture of hamamelis in a little water before the two principal meals. In case of a fibroma he alternates the two pituitary weeks with other organotherapy, and may conclude with roentgen treatment. Congestions and excessive functioning of the ovaries or

thyroid may likewise benefit by pituitary treatment, as also certain types of headache, even those suggesting false brain tumors, with exacerbations at the menstrual periods. It seems in these cases as if the endocrine upset had induced congestion in the pituitary body and that this congestion was what causes the headache. The action of pituitary treatment is not restricted to the genital organs; it may attenuate and suppress the hot flashes and sudden sweats of the menopause and other symptoms of ovarian insufficiency. It seems to promote sleep, appetite and diuresis, and combat asthenia.—J. Am. M. Ass.

**(HYPOPHYSIS) A case of dystrophia adiposogenitalis in a man after trauma of the skull (Ein Fall von Dystrophia adiposo-genitalis bei einem Manne nach Schädeltrauma).** Goldsteig. Berl. klin. Wchnschr., 1919, **56,** 958; Münchner med. Wchnschr., 1919, **66,** 1009.

A short note on a case. The temperature showed an inclination to rise. From time to time temperatures up to 42.3° C. (107.6 F.) were observed; the pulse stayed at 70. Probably the centre for heat regulation was disturbed.—J. K.

**(HYPOPHYSIS) Conditions in "hyperhypophysized" animals. (Ueber Befunde bei hyperhypophysierten Tieren).** Hofstätter (R.), Monatsschr. f. Geburtsh. u. Gynäk. (Berlin) 1919, **19,** 387.

Results from transplantation and from feeding were negative. Injections of "pituitin" were given to 70 rabbits. The doses (1 cc. each) were given every two days, until from ten to forty had been given. The results were as follows: 1, Hypertrophy of the heart, with hyperemia of all the organs; 2, Diuresis not influenced; 3, No effect on growth or on skeleton; 4, Decrease of the colloids of the thyreoid; 5, Hypertrophy of the adrenals; 6, Slight hypertrophy of the hypophysis; 7, Hastening of ovulation and spermatogenesis in young, but no such effects on full-grown animals; 8, No effect on the atrophy of the uterus after castration; 9, Development of mammary glands stimulated; 10, Sexual stimulation. The author concludes that the hypophysis aids embryonic development, "protects" the sex glands and their functions, as well as the milk glands, and inhibits the thyreoid. Hypophysis medication is indicated for general hypoplasia, amenorrhea and Graves' disease.

—E. R. H.

**(HYPOPHYSIS) Epilepsy combined with endogenous adiposity [Epilepsie kombiniert mit endogener (hypophysärer?)**

**Fettsucht].** Ibrahim. Münchener med. Wchnschr., 1919, **66,** 1069.

A girl of twelve years suffered from epilepsy. After the first fit adiposity began. The Wassermann reaction was negative; there was no increased brain-pressure; blood-pressure was low. The skin showed abnormal pigmentation. Adrenalin injection did not produce glucosuria. After 100 grams of glucose a trace of sugar was found in the urine. The sella turcica was not enlarged, but showed the form of a rhombus. The patient was mentally deficient. The blood serum gave a positive Abderhalden reaction with hypophysis, ovary and thyroid and a negative reaction with adrenals and kidney.

—J. K.

**(HYPOPHYSIS) An experimental investigation of the pharmacologic properties of the active principle of commercial pituitary extracts, and the comparative action of histamine.** Jackson (D. E.) and Mills (C. A.), J. Lab. & Clin. Med. (St. Louis), 1919, **5,** 1-27.

The active principle of the posterior portion of the pituitary gland is a simple body of the sympatho-mimetic amine type which, in the dog, produces contraction of the uterus but fails to contract the bronchi. This is probably due to action of the substance on certain nervous elements and not a direct muscular action. Certain commercial preparations of pituitary gland contain small, variable proportions of histamine which might exert some therapeutic action, but it is not a necessary constituent of first-class preparations of posterior portion of the pituitary. It is probable that the action of histamine on the bronchioles of spinal dogs can be used as a commercial test for the presence of small amounts of this substance in ordinary commercial extracts. For obstetrical uses pituitary extracts have obvious clinical advantages over the broncho-constricting and blood pressure lowering histamine.—B. T. S.

**HYPOPHYSIS, The relation of—to glycogenolysis.** Keeton (R. W.) and Becht (F. C.), Am. J. Physiol. (Balt.), 1919, **49,** 248-253.

The authors show that stimulation of the hypophysis in dogs causes hyperglycemia independently of the ether used for anesthesia. This hyperglycemia is absent after transection of the cord at the level of the second thoracic vertebra and after section of the splanchnics, but persists after section of the nerves in the hepatic pedicle, i.e. where the nerve supply to the adrenals is not interfered with. Consequently, if a hormone

is liberated by stimulation of the hypophysis, it must have a central action. Following hypophysectomy a transitory hyperglycemia, persisting three to five hours, occurs. After this the sugar level remains normal until death. The authors favor the view that the pathway is a nervous one mediated through the splanchnic nerves to their terminations in the adrenals and liver. Also, they are of the opinion that the hypophysis does not affect glycogenolysis but is concerned with the utilization of sugar by the organism.—L. G. K.

**(HYPOPHYSIS) Hypophysaire diabetes.** Koopman (J.), Ned. Tijdschr. v. Geneesk. (Haarlem), 1919, **63** (II), 1071.

A short abstract of an article published in Endocrinology, **3**, 485.—J. K.

**(HYPOPHYSIS-PANCREAS) Acromégalie et diabète.** Labbé (M.) and Langlois (S.), Bull. Soc. Méd. des Hôp. (Paris), 1919, **43**, 229-234.

Observations are herein reported of a typical case of acromegaly, in a miner of 48, but superimposed upon this were polyuria and glycosuria. Neither polyuria nor glycosuria were in any definite way influenced by hypophysis medication, either by whole gland or by extracts of posterior lobe. On the other hand, reduction of the carbohydrate intake or fasting for three days cured the glycosuria without affecting the polyuria. Furthermore this particular patient did not lose weight nor become emaciated and had in effect a high tolerance for sugar.

The polyuria was thought to be due, following the ideas of Loeb, to irritation of the centers at the base of the brain by the enlarged hypophysis. The glycosuria was thought to be due in part to irritation to this region and in part was thought to be alimentary glycosuria in the ordinary sense.—A. L. T.

**(HYPOPHYSIS) Antipituitary serum. In arteriosclerosis and diabetes mellitus. (Preliminary communication.)** Laura (C. L ) N. Y. Med. J. (N. Y.), 1919, **110**, 713.

A preliminary report of the action of serum obtained from the horse following immunization with extracts of posterior and infundibular pituitary, upon blood pressure and sugar metabolism. This "antipituitary serum" was used on about 40 patients who received several intramuscular injections, in doses of from one to three cc., at intervals of from two to five days. The larger number of patients were diabetics, some were suffering from arteriosclerosis, some from various diseases and

two were normal. In all of the patients except two, and after every injection, the blood pressure was affected with small as well as large doses. Within thirty minutes following the injection, the blood pressure became reduced by 15 to 20 mm. and gradually reached a maximum depression in one or two hours and remained down for several hours. Of 30 patients suffering with diabetes mellitus treated with the serum, eight did not respond, fourteen had a complete disappearance of sugar from the urine, while the intake of carbohydrates was notably increased, and eight had a diminution of glycosuria. Polyuria commonly disappears with rapidity, even in the most unfavorable cases.—H. W.

**(HYPOPHYSIS) An explanation of acromegaly (Ein Streiflicht auf die Akromegalie).** Lentz (F.), Münchener med. Wchnschr., 1919, **66,** 992.

The author tried to answer the question why in acromegaly do the hands, feet, nose, ears and chin grow. He tries to find a relation with the experiments of Schultz, who experimented on Russian rabbits with white hair, except on the ears, where it is black. If a part of this white hair is removed and the animal is kept in the cold, the new hairs on this spot are black. Because of these experiments Lentz believes that hands, feet, nose, ears and chin grow in acromegaly because they are the coldest parts of the body.

(The experiments of Schultz are interesting, but the conclusion of Lentz is at least unproved, not to use another word).—J. K.

**(HYPOPHYSIS) A method of tissue analysis: Applied to the lobes of cattle pituitaries.** MacArthur (C. G.), J. Am. Chem. Soc., 1919, **41,** 1225-1241.

The method of separation into proteins, lipins, and extractives is based upon the method of W. Koch (J. Am. C. S. **31,** 1329). The original method has been simplified and made available for amounts of material extending from 10 gms. to as low as 2 gms. Methods are given for the determination of Ca, Mg, total N, ammonia N, urea N, amino N, creatinine, creatin, uric acid, total S, S as sulfate, neutral S, extractive S, neutral P, lipin residue N and P, cholin N, absorbed iodine, sugar, cholesterol, humin-N, in the three fractions. Complete analyses of the anterior and posterior lobes are given.

The anterior lobe has 2.4% more solids, 4% more protein, 0.9% less lipins, 0.9% less extractives than the posterior lobe. The distribution of the various elements and compounds in the

protein fraction indicates a close similarity in nature of the proteins of the two lobes. Except for the small amount of sulfatides in the hypophysis the distribution and amounts of the various lipins are similar to those of the cortical gray matter. The extractives predominate in the posterior lobe. This predominance consists mainly in the non-phosphate P, amino N, and undetermined N fractions. The two latter may be present in the pressor compound.

The chemical composition of the hypophysis resembles the gray matter of the brain or young nervous tissue in most respects. There are points of resemblance to the thyroid and spleen, quite a few to the liver, but practically none to the connective tissues, muscle, or white matter of the brain.

In those respects in which the two lobes differ the posterior is more like the gray matter than the anterior. Both lobes resemble each other more closely, than either resembles any other tissue. It cannot be stated that the pituitary is more like unmedullated nervous tissue than it is like undifferentiated pus cells. It can be assumed as an hypothesis that the partly differentiated embryological materials, after union of the two parts, develop together, resulting in a similarity of composition.—V. K. L.

**(HYPOPHYSIS) The effect of feeding pars tuberalis and pars anterior proprior of bovine pituitary glands upon the early development of the white rat.** Marinus (C. J.), Am. J. Physiol. (Balt.), 1919, **49**, 238-247.

A group of 53 rats was fed upon pars anterior proprior of the pituitary gland, a second group of 37 animals upon pars tuberalis, while a control group of ten received beef muscle. During the 12 weeks of feeding the rats of the first group exhibited an increased growth rate accompanied by a more rapid development of the reproductive system, evidenced by gross and microscopic hypertrophy of the organs and by the earlier birth of young. In the pars tuberalis-fed rats there was no change in the sexual development as compared with that of the control group. The growth rate was slightly slower in the second group, due perhaps to the smaller amount of meat received. The author concludes that his study does not show that any of the functions ascribed to the anterior lobe as a whole are due to the pars tuberalis.—L. G. K.

**(HYPOPHYSIS). Report on the use of tethelin.** Mayo (Helen M.), Med. J. Australia (Sydney), 1918, **5**, 413.

This is a report of the treatment of an electrical burn on the leg of a long-standing diabetic, with combined injections

and applications of "tethelin." The burn had been complicated by the application by the patient of carbolic solution. The tethelin was administered in 100 milligram doses divided between the two methods of procedure for ten days, when healing was practically complete. No further trouble was experienced with the leg, but the patient died four months later, insane, and in coma.—F. S. H.

**(HYPOPHYSIS) The possible cause of hereditary optic atrophy.** Pancoast (H. K.), Am. J. Roentgenology, 1919, **6,** 17.

Fisher has advanced the theory that this disease might be due to a transient disorder of the pituitary body with enlargement occurring at definite epochs of the sexual life. With the idea that the roentgen examination would seem to be the most certain means of proving this point, provided the enlargements were sufficient and of a necessary prolongation to produce a sellar deformity, the author presents his studies of the affected members of two families. These studies tend to lend weight to Fisher's theory of the etiology of this disease, but cannot be regarded as proof positive.—J. F.

**(HYPOPHYSIS) Operation der Hypophysistumoren.** Piffl. Berl. klin Wchnschr., 1919, **56,** 863; Wiener klin. Wchnschr., 1919, **32,** 870.

Only of technical surgical interest.—J. K.

**(HYPOPHYSIS) Action of endo-hypophysin and infundibulin on the pregnant uterus (L'azione dell' endo-ipofisina e dell' infundibulina sull' utero gravido).** Pugliese (A.) Terapia, 1916, No. 22 (Reprint, p. 16.)

The former preparation is an extract of the whole pituitary; the latter of the infundibulum with a portion of the pars intermedia. Although the non-pregnant uterus of the guinea-pig and rabbit reacts well enough when isolated in a bath of Ringer's solution it does not respond readily in situ to a hypodermic injection. For this purpose a pregnant uterus is necessary, and since the therapeutic method of administration is a hypodermic one, the author considers this method also necessary for laboratory testing. Hence he employs pregnant guinea-pigs or rabbits, removes the fetuses and allows a uterine horn to protrude through a small opening in the abdominal wall into a myograph chamber jacketed with warm water.—Physiol. Abst., **3,** 386.

**HYPOPHYSIS, On an uncommon disease caused by an adenoma of the— (Über ein ungewöhnliches Krankheitsbild bei Hypophysenadenom).** Reichmann (V.), Deutsches Archiv. f. klin. Med. (Leipzig), 1919, **130,** 133; Münchener med. Wchnschr., 1919, **66,** 1103.

Two cases are described with the same symptoms: red swollen face, protusion of the eyes without other symptoms of Graves' disease; no goitre, bradycardia, myasthenia, general cachexia, edema of the legs; slight glycosuria, no albuminuria, arteriosclerosis, high blood pressure (without Bright's disease), osteoporosis of the vertebral column. One patient died. The post-mortem examination showed an eosinophil adenoma of the hypophysis. The second patient showed an abnormal shadow in the place of the sella turcica on the roentgenogram. Probably the disease may be considered as a hyperfunction of hypophysis and adrenals and a hypofunction of the thyroid.

—J. K.

**(HYPOPHYSIS) Hypophysäre Kachexie.** Reye. Berl. klin. Wchnschr., 1919, **56,** 790.

A woman with general cachexia and oedema was treated with hypophysis with good success. Her treatment was not continued and in four months the patient became seriously ill with cachexia, oedema and a blood pressure of 80 mm. Again treatment with hypophyses gave splendid result, but, though the oedema disappeared, the patient gained enormously in weight.—J. K.

**(HYPOPHYSIS) Signs and symptoms of hypopituitarism.** Roberts (Stewart R.), Proc. Southern Med. Assn., J. Am. M. Assn. (Chgo.), 1919, **73,** 1795.

Undergrowth, dwarfism, dysgenitalism, feminine hirsuties, feminine type of skeleton, lack of secondary sexual characteristics, genital atrophy and impotence, headaches, languor and weakness may appear in varying degrees in different cases at different periods. The classic signs and symptoms of hypopituitarism are subnormal temperature, dry skin, adiposity, low blood pressure, slow pulse, constipation, amenorrhea, drowsiness and inactivity. Lack of attention, impairment of memory, actual dulness, and mild psychoses to actual convulsive seizures with epileptic attacks may occur. The cause may be glandular deficiency of one or both lobes, a pituitary tumor with damage

of the gland, or a neighborhood tumor or hydrocephalus with pituitary pressure. The symptoms of intracranial tumor may be more prominent than those of pituitary deficiency. Infantilism, dysgenitalism and obesity, and symptoms of intracranial tumor, warrant pituitary study.—Quoted.

**(HYPOPHYSIS) A metabolism study in a case of diabetes insipidus.** Rosenbloom (J.) and Price (H. T.), Am. J. Dis. Child. (Chgo.), 1916, **12**, 53-60.

The writers recognize two types of diabetes insipidus in children: (1) primary or idiopathic cases, including those in which there is no evident organic basis for the disease; (2) symptomatic, including those cases in which some organic disease is present in the brain or elsewhere. According to them, there are three theories as to the etiology of this condition, as follows: (1) that it is due to a lack of ability of the kidneys to concentrate the urine; (2) that primary polydipsia exists with normal kidney function; (3) that it is a polyuria, purely symptomatic in origin, produced by stimulation of the kidneys by many causes, but in some cases by a hypersecretion of the hypophysis. They give a brief review of the literature on the relationship between the hypophysis and diabetes insipidus.

—M. B. G.

**(HYPOPHYSIS) Pituitary standardization. The relative value of infundibular extracts made from different species of animals and a comparison of their physiological activity with that of certain commercial preparations.** Roth (George B.), U. S. Pub. Health, Hygienic Lab. Bull. No. 109 (Washington), 1916.

The determination of the activity of infundibular extracts made from the pituitary body obtained from various species of mammals—namely, cattle, sheep, horses, hogs, rabbits, cats, and dogs—was made by both the blood pressure and the isolated uterus methods, and it was found that the infundibular extracts made from cats or dogs were more active than similar extracts made from the other species of mammals. An individual variation was shown in extracts made from the same species of mammals. Commercial infundibular extracts examined in the same way showed a variation of 800 per cent by the blood pressure method and of 1,000 per cent by the isolated uterus method. A commercial preparation of infundibular extract which contained chlorbutanol as a preservative was shown to depress the motility of the isolated intestine of the rabbit when used in concentrated solution.

It was concluded that the activity of infundibular extracts on the isolated uterus of the virgin guinea-pig should not be taken as an index of their activity on the blood pressure. Infundibular extracts made from the pituitary bodies obtained from cattle, horses, hogs, cats, dogs, and rabbits differ quantitatively in their activity. The infundibular lobe of the pituitary body of cats, dogs, and hogs contains a greater amount of active materials than from cattle, sheep, horses, or rabbits. Commercial infundibular extracts vary widely in their physiological activity. The motor depression of the isolated intestine which is caused by certain commercial infundibular extracts is due in certain instances to the depressing effect of the preservative chlorbutanol.—Author's Summary.

**HYPOPHYSIS, Development of the form of the human—. (Formentwickelung der menschlichen Hypophysis cerebri).** Rudel (E.), Anat. Heft. (Weisbaden), 1918, **55**, 187.

Technical description of the hypophysis, as indicated by the title.—E. R. H.

**(HYPOPHYSIS) Hypophysentumoren.** Saenger. Berl. klin. Wchnschr., 1919, **56**, 789.

Demonstration of two patients in whom tumors of the hypophysis were extirpated. In the first case neither the amaurosis nor the dystrophia adiposo-genitalis were beneficially influenced, but the patient felt better. In the second case the eye symptoms became first better after the operation, but returned later on and acromegaly developed.—J. K.

**HYPOPHYSIS, X-ray treatment of tumors of the—and acromegaly with temporal hemianopsia (Zur Röntgenbehandlung der Hypophysistumoren und der Akromegalie mit temporaler Hemianopsie).** Schäfer (F.), Deutsche med. Wchnschr. (Berlin), 1919, **45**, 981; Berl. klin. Wchnschr., 1919, **56**, 886.

A short note. Of eight cases treated with X-rays, six were largely improved. It is most important to place the head in a way that the hypophysis is situated in the focus of the X-rays.—J. K.

**HYPOPHYSIS. Operation der Hypophysistumoren.** Schloffer, Berl. klin Wchnschr., 1919, **56**, 863.

Only of surgical interest.—J. K.

**(HYPOPHYSIS) The action, use, and abuse of pituitrin.** Schulze (A. G.), Jour.—Lancet (Minn.), 1919, **39**, 584-589.

Nothing new—H. W.

**(HYPOPHYSIS) Post-mortem examination of a dwarf. (Sektionsergebnis bei einem Zwerg).** Simmonds. Berl. klin. Wchnschr., 1919, **56**, 790.

The post-mortem examination showed atrophy of the testicles; the anterior lobe of the hypophysis was nearly completely destroyed by cysts. The posterior lobe was normal.
—J. K.

**(HYPOPHYSIS) Case of acromegaly.** Soner, Med. J. S. Africa (Johannesburg), 1918, **13**, 102-104.

A clinical presentation and discussion of a case presenting a syndrome indicative of myxoedema, but which on X-ray analysis showed undoubted acromegalic characteristics, though with some accompanying thyroid derangement.—F. S. H.

**(HYPOPHYSIS) On the use of very small doses of pituitrin in inducing labor at term in combination with nitrous oxide anaesthesia to alleviate the labor pains.** Stein (A.), Trans. Am. Gyn. Soc., Am. J. Obst. (N. Y.), 1919, **80**, 471.

No new data.—H. W.

**(HYPOPHYSIS) Dyspituitarism, with limitation of the visual fields. Symptoms disappearing under the use of internal glandular therapy, with a return of the visual fields to normal.** Timme (Walter), Arch. Opth., 1917, **46**, 151-153.

This patient came under observation after suffering six years from constant headaches and diminished vision. On examination contracted visual fields were found. A diagnosis of pituitary enlargement was made with dyspituitary symptoms. Treatment was with extracts of thyroid and pituitary and, because of the low blood pressure manifested, whole suprarenal gland was administered with excellent results.—J. H. L.

**(HYPOPHYSIS) A case of pituitary tumor treated by operation.** Whale (H. L.), Lancet (Lond.), 1919 (ii), 11-12.

Sellar decompression and removal of endotheliomatous tissue from the anterior lobe of the pituitary gland was followed by great improvement in the previous pressure symptoms.—L. G. K.

**(INTERNAL SECRETION) Phenomena of transformation of larval tissues into reserve tissues, observed during the metamorphosis of some metabolan insects. (Phénomènes de transformation de tissus larvaires en tissus a réserves observés pendant les métamorphoses des insects metaboles.** Bordage (E.), C. r. Acad. d. Sci. (Paris), 1917, **165,** 477.

Bordage observed that in insects, the developmental cycle of which includes a chrysalis stage, the larval tissues during the chrysalis stage undergo a direct (without the action of phagocytes) and complete histolysis (lyolysis of Anglas) in the course of which they are entirely dissolved. It seems that this histolysis is exactly equivalent to the histolytic processes known to take place during the metamorphosis of amphibians. (In the latter case we are fairly certain that the histolysis of the larval tissues is caused by the thyroid hormone. Bordage's suggestion that in insects a histolytic secretion may be excreted into the body fluids by some organ, seems, therefore, to have some already well established facts in favor and it would be of greatest importance to look for those organs or tissues which might excrete such substances in insects. Possibly we will find here the predecessors of the vertebrate thyroid gland.) —E. U.

**INTERNAL SECRETIONS, Progress in the knowledge of— (Fortschritte in der Lehre von der inneren Sekretion).** Pütter (A.), Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1008.

A general review of some well known facts of endocrinology.—J. K.

**(INTERNAL SECRETIONS) Exophthalmos in leukemia.** Schioetz (C.), Tidsskr. f. d. norske laegeforen., 1916, —, —.

Details are given of two cases of acute lymphatic leukemia, where exophthalmos was a prominent symptom. This is demonstrated anatomically to be due to edema of the fatty tissue in the orbits. The various toxic and endocrine causes of exophthalmos are discussed; the explanation is offered that certain toxic substances, especially aromatic amino-compounds, have an elective effect on the orbital fat.—K. M.

**LIPODYSTROPHIA progressiva, A new case of—.** Weber (F. P.) and Gunewardene (T. H.), Brit. J. Child. Dis. (Lond.), 1919, **16,** 89.

Weber reports another case of this rare condition. The

patient was a girl of 12½ years of age, who since the age of 7½ years, has been losing the subcutaneous fat over her face, neck, upper extremities and trunk as far down as the pelvis, being emaciated in these parts, but normal below the hips. The change occurred following attacks of measles, pertussis and pneumonia, in rapid succession. The previous case of this condition which was reported by Weber was abstracted in Endocrin. 1917, **1**, 481.—M. B. G.

**MYOTONIA ATROPHICA.** Slecht. Berliner klin. Wchnschr., 1919, **56**, 405.

Three typical cases. All three showed cataract, loss of hair, atrophy of skin and atrophy of the thyroid and testes.
—J. K.

**OSTEOMALACIA, A case of infantile—(Ein Fall von kindlichem Osteomalazie).** Blencke, Münch. med. Wchnschr., 1919, **66**, 948.

Of no direct endocrine interest.—J. K.

**OSTEOMALACIA, An epidemic of— (Ueber gehauftes Auftreten von Osteomalazie).** Partsch (F.), Deutsche med. Wchnschr. (Berlin), 1919, **45**, 1130.

The same epidemic that has been observed in Vienna has been seen in Dresden. The description is of no direct endocrine interest.—J. K.

**(OSTEOMALACIA) Familial starvation-osteomalacia (Familäire Hungerosteomalazie).** Schlesinger (H.), Wiener klin. Wchnschr., 1919, **32**, 929.

The author demonstrated two sisters and a mother and a daughter with osteomalacia. The latter two patients had large goitres.—J. K.

**(OVARY) On the origin of the corpus luteum of the sow from both granulosa and theca interna.** Corner (G. W.), Am. J. Anat. (Phila.), 1919, **26**, 117.

The ovary of the sow possesses certain advantages for the solution of this problem. The paper is based upon a large series in which the stage of the reproductive cycle was determined by observation of the living animals and their ova. The results may be summarized as follows: In swine the membrana

granulosa is retained intact after the rupture of the Graafian follicle. Its cells increase in size without division, the cytoplasm becomes laden with lipoid substances, and they become the larger elements commonly called "lutein cells" in the fully formed corpus luteum. The membrana granulosa is invaded by blood capillaries from the theca interna which ramify to form an extensive vascular plexus throughout the new structure. The lipoid-laden cells of the theca interna are increased in number by mitotic division, lose many or all of their fatty inclusions, and pass into the corpus luteum to become lodged between the granulosa cells throughout the whole structure. There is no evidence that cells of the theca interna are ever converted into fibroblasts of the usual spindle-cell type or that they lay down the fibrils of the close-meshed reticulum which is present in the corpus luteum. There appears to be good evidence that some of the theca interna cells persist throughout pregnancy as distinct elements of the corpus luteum, but the exact fate of all of them cannot be learned by present methods because of the confusing resemblance between some of the theca and some of the granulosa derivatives. (Author's abstract.)

**(OVARY) Uterine haemorrhages and their relation to internal secretion (Über Gebärmutterblutungen und ihre Beziehung zur inneren Sekretion).** Flatau, Münch. med. Wchnschr., 1919, **66**, 1069.

Gynecologists too often forget that many uterine haemorrhages find their origin in the ovary. In these cases treatment with the curette is a failure. Treatment with corpus luteum preparations may give good success in these cases.—J. K.

**(OVARY) Two cases of hypernephroma of the ovary.** Gordon (A. K.), Brit. Med. J. (Lond.), 1919 (ii), 495.

Not of endocrine interest.—L. G. K.

**(OVARY) Are the operative procedures done for dysmenorrhea and sterility justifiable in the light of developmental study?** Holden (F. C.), Am. Jour. Obst. (N. Y.), 1919, **80**, 415-420.

Report of beneficial results following endocrine therapy in cases of sterility and dysmenorrhea.—H. W.

**(OVARY) Preliminary report on the influence of alcohol and nicotine upon the ovary.** Ogata (S.), J. Med. Res. (Boston), 1919, **40**, 123-127.

No apparent changes were found in the ovaries following repeated injections of ethyl alcohol into the ear vein of rabbits, though in some cases there were fewer developing Graafian follicles than in the normal, in addition to inhibition of growth of the ovary. Similar experiments with extract of cigar tobacco resulted in no apparent changes in the ovary either macroscopically or microscopically.—Chem. Abst., **13**, 2924.

**(OVARY) Absence of uterus, fallopian tubes, one ovary and vagina, with one large central kidney.** Parakh (F. R.), Brit. Med. J. (Lond.), 1919, (ii), 496.

The condition found during an exploratory coeliotomy is indicated in the title. The woman was perfectly healthy, except that she had never menstruated.—L. G. K.

**(OVARY) Ovulation, conception and abitrary impregnation. (Ovulation, Konzeption, und willkürliche Geschlechtsbestimung).** Ruge (C.), Verhand. der Gesall. f. Geburtsh. u. Gynäk zu Berlin, Ztschr. f. Geburtsh. u. Gynäk (Berlin), 1919, **81**, 256.

An extended series of clinical observations, the number of which is not recorded, has led the author to the conclusion that ovulation follows the first half of the menstrual cycle. It can begin as soon as the progressing corpus luteum, which during its growth inhibits the complete development of other follicles, begins to retrogress, and is dependent as much upon internal factors still unknown to us as upon external, among which, apparently, the sexual stimulus plays a significant part. The optimum conception time is after menstruation.—F. S. H.

**(OVARY) Osteomalacia in an antelope.** Schumann (E. A.), Trans. Obst. Soc. Philadelphia, Am. Jour. Obst. (N. Y.), 1919, **80**, 223.

A pregnant antelope was so weak that it could not stand. It miscarried and later regained health and at the end of six months again became pregnant. Weakness became marked and the animal finally died. An autopsy revealed cystic ovaries and a partly developed embryo in the uterus. The skull was typical of osteomalacia, the pelvis was distorted and the bones throughout were flexible. Osteomalacia appears to be common in wild animals held in captivity. The author is inclined to believe that the condition is essentially the result of improper metabolism. However, the occurrence of the symptoms of

osteomalacia with pregnancy seem to indicate that the disease is in some way associated with pathological states of the primary reproductive organs.—H. W.

**OVARY, Experimental degeneration in the—of the fowl, caused by altered surroundings. [Ueber experimentelle durch veränderte äussere Bedingungen hervorgerufene Rückbildungsvorgänge am Eierstock des Haushuhnes (Galeus domesticus)].** Stieve (H.), Arch. f. Entw. (Berlin), 1918, **44**, 530.

Actual anatomical changes (degeneration of follicles) take place in the ovary of a fowl kept in close confinement. The author concludes that this is not due to absence of sexual stimulation, though this possibility is not absolutely excluded. Too much food and too little exercise caused fatty degeneration in some cases, but in the majority of instances no other cause than psychic disturbance can be assigned.—M. M. H.

**(PANCREAS) Diabetic lipoidemia.** Bang (Ivar), Biochem. Ztschr., 1919, **94**, 359-391.

From an extended study of a number of cases B. concludes that there is not necessarily a relationship between carbohydrate tolerance and lipemia. Experiments also indicate that diabetic lipemia is of alimentary origin. Coma is an exception. Hyperlipemia is not of pure alimentary origin. That the diabetic organism cannot take care of the resorbed fat is probably due to the liver. Since this liver insufficiency cannot be associated with acidosis or with hyperglycemia, it stands rather alone and B. questions the significance of lipemia. Is it a good or bad prognostic symptom?—Chem. Abst., **13**, 3239.

**(PANCREAS) The dietetics of diabetes and glycosuria.** Brown (W. Langdon), Practitioner (London), 1919, **103**, 88-99.

The author, in addition to an interesting review of modern methods of treating diabetes calls attention to "non-diabetic glycosuria." Overaction of either the thyroid or the pituitary lowers carbohydrate tolerance, and may excite frank glycosuria. He considers the glycosuria of pregnancy (as distinct from lactosuria) probably due to its stimulating effect on the thyroid and pituitary.—H. L.

**(PANCREAS DIABETES) Glycosuria in pregnancy.** Cameron (M. H. V.), Can. Med. Assn. J. (Toronto), 1919, **9**, 717-722.

In 468 cases of pregnancy, five cases of glycosuria were found. In four of these the sugar was identified as glucose and in the other, as the patient died of diabetes, the sugar supposedly also was glucose. Consequently finding of sugar in the urine during pregnancy must be regarded seriously and not lightly dismissed as a probable lactosuria. Where glycosuria exists, true diabetes may be about to manifest itself or may be already in existence. Regulation of the diet keeps the symptom in abeyance. A careful selection of anesthetic and any means possible to lessen the shock of delivery helps to prevent the onset of such changes in the endocrine system, already strained beyond the normal, as indicated by the glycosuria and which might result in diabetes. Should the glycosuria be controllable by diet regulation, frequent examination of the urine may be sufficient to protect the patient during gestation. This does not, however, decide whether her diabetes is under control because of the possibility of foetal hormones, functioning in the maternal economy, nor does it differentiate a glycosuria due to hyperalimentation or secretion of inverted lactose. The only means of arriving at definite conclusions is by estimation of the sugar in the blood.—L. G. K.

**(PANCREAS) Diabetes, The fasting treatment of—.** Cammidge (P. J.), Brit. Med. J. (Lond.), 1916, (ii), 160-161, 243.

Contains a table showing the carbohydrate content of various foods to be used in the fasting treatment of diabetes. Excellent results from this method are reported.—L. G. K.

**(PANCREAS DIABETES) Glycosuria in elderly persons.** Cammidge (P. J.), Brit. Med. J. (Lond.), 1919, (i), 112-113.

Cammidge criticizes the view of Rankin (see abstract in this number), that a moderate amount of sugar in the urine of elderly persons need not cause alarm. In the author's experience there are two types of such persons, and the difference depends largely upon the sugar content of the blood. Even a moderate excretion of sugar associated with hyperglycemia leads in the course of time to complications, whether the patient be young or old, whereas glycosuria unattended by an excess of sugar in the blood is not likely to give rise to trouble or shorten life, especially if, as often happens in elderly persons, the reducing substance in the urine is not really a sugar but the ketonic acid previously described by the author under the name of "pseudo-laevulose."

The success of the Allen treatment of diabetes in elderly persons depends upon individualization of the treatment and

education of the patient, so that he may follow his diet intelligently. Such persons do not stand starvation well, but as a rule, actual fasting is not necessary to secure a normal blood sugar and a sugar-free urine if a carefully arranged system of dieting is followed.—L. G. K.

**(PANCREAS) Dehydration of blood and organs in diabetic coma. (La déshydratation du sang et des organes dans le coma diabétique).** Chauffard (A.), Le Conte, Darie. Presse Méd. (Paris), 1917, **25,** 185.

A careful study was made of two instances of diabetes mellitus in which there was found definite evidence of dehydration in various tissues. The blood was characterized by a polycythemia and increase in density. In other tissues an increase in density or decreased water content of kidneys, liver and pancreas was found. The most marked changes in tissue density were in the pancreas.—A. L. T.

**(PANCREAS) Disappearance of glycosuria in diabetics during intercurrent infectious diseases. (De la disparition de la glycosuria chez les diabetiques ou cours des malades infectieuses intercurrents.)** Cottin (E.) and Saloz (M. C.), Arch. d. mal. de l'appar. digest (Paris), 1916-1918, **9,** 371-383.

The authors report that in four diabetics with glycosuria the occurrence of an intercurrent infection with fever was accompanied by a cessation of the urinary sugar excretion. This they consider may be due to an abnormal destruction of protein; an alteration in the glyco-regulating mechanism by virtue of the septic process; an activation of combustion by the increased temperature; or, as seems more plausible, consumption of the glucose by the infectious agent.—F. S. H.

**(PANCREAS) Diabetes mellitus of four years standing followed by pulmonary tuberculosis with apparent cure of both as told by patient.** Cram (E. A.), Ky. Med. J. (Bowling Green), 1919, **17,** 408-409.

Content indicated by caption.—H. W.

**(PANCREAS) Diabetes mellitus.** Densten (J. C.), N. Y. Med. J. (N. Y.), 1919, **110,** 613-615.

There is little or no interference within the animal economy of a diabetic with the ingestion and metabolism of animal nitrogenous foods and some vegetable proteins. The major

metabolic fault lies in the noncleavage of sugar into alcohol or its radicles. Hence, alcohol is indicated in amounts sufficient fully to account to the system the lack of nourishment which the sugar should furnish if split further by a normally constituted system. The withdrawal of carbohydrates from a diabetic of any age is not advisable. Starvation only causes the body to utilize its own fat. Moreover, such procedures only tend to result in inanition. Diabetes should not be considered a disease per se, but rather a symptom of some existing constitutional organic abnormality or disease. It may be a sequel of syphilis, or it may be traced to some viscus as the pancreas, liver, spleen, appendix, etc., or to a deranged function of the pituitary body. Hence, the etiology of diabetes should be sought and treated.—H. W.

**(PANCREAS) Diabetes mellitus.** Edgar (T. W.), N. Y. Med. J. (N. Y.), 1919, **110**, 612-613.

Starvation of diabetics is not applicable in all cases and should not be used empirically. Emaciation and lowered bodily resistance contraindicate starvation. The emaciated or cachetic diabetic who has resorted time and again to starvation with ever decreasing tolerance does better if carried along on his last assimilation limit for a short time. The intermittent starvation of animals first results in an increased ability to assimilate sugar, but is later followed by a decrease as time advances, that is, after body weight has been sacrificed, hence a decreased resistance has a direct bearing on the carbolytic action of the sugar enzyme or enzymes. The diabetic patient, although rendered aglycosuric by starvation, will require a longer period of time to attain his previous point of tolerance than if granted a short reprisal and allowed to continue his last diet in spite of the urine showing sugar.

Specific serum therapy (Edgar serum) is highly recommended in the treatment of diabetic cases. No discussion appears relative to this serum.—H. W.

**(PANCREAS) Edgar serum treatment of diabetes mellitus.** Edgar (T. W.), West. Med. Times (Denver), 1919, **39**, 172-174.

Treated elsewhere.—H. W.

**PANCREAS, Relation of the—to the diabetic state.** Ervin (D. M.), J. Lab. & Clin. Med. (St. Louis), 1919, **4**, 711.

The pancreatic diabetic state is characterized by several pathological changes—absence of glycogen, hyperglycemia,

fatty changes, acetone bodies and glucose in the urine and a lower respiratory quotient. Experiments were performed to test the glucose consumption in the diabetic animal. The latter was produced by the removal of the pancreas. The results showed that, while after depancreatization, the blood sugar increased in amount, the actual oxidation by the tissues is practically the same as before the operation. The hyperglycemia is readily explained by assuming a glycogenetic function for the pancreas through an internal secretion of the islands of Langerhans.

The internal secretion contains an enzyme which resembles that of the external secretion. It is assumed that the enzyme acts by stimulating a reversible chemical reaction. The external secretion reduces the starch in the intestine to glucose while the internal secretion poured into the portal circulation reverses the action upon the absorbed glucose, synthesizing it into glycogen which is stored by the liver. By clamping the pancreatic vein and injecting glucose solution in the small intestine, a marked hyperglycemia was produced. A controlling experiment did not show this rise. The same results occurred with the removal of the pancreas.—B. T. S.

**(PANCREAS) Diabetes with pancreatic insufficiency. Treatment by glandular extracts; selective therapeusis of the external secretory function of the pancreas (Diabète avec insuffisance pancréatique. Traitment opothérapique; disjonction thérapeutique des secretions externe du pancréas).** Faroy (G.), Bull. Soc. méd. des Hôp. (Paris), 1917, ~~41, 235~~. A 3.234

A case of diabetes is described running a typical course until there appeared, in addition to endocrine deficiency, a deficiency of the external secretion of the pancreas. The exocrine dysfunction of the pancreas was alleviated by the administration of pancreatic extract. The true diabetes, however, was not in the least affected by this therapy. The case is illustrative of the independence of the endocrine functions of the pancreas, and of the fact that the exocrine function may be replaced, or secretion stimulated by exhibition of pancreatic extracts without any diminution of the glycosuria, polyuria and other signs of true diabetes mellitus.—A. L. T.

**(PANCREAS) Notes on the starvation treatment of a young diabetic.** Fenwick (P. C. C.) Lancet (Lond.), 1919 (i), 299.

Record of a case of diabetes in a boy of 16 who recovered under the starvation treatment.—L. G. K.

**(PANCREAS DIABETES) Hyperglycaemia and glycosuria.** Hamburger (H. J.), Brit. Med. J. (Lond.), 1919 (i), 267-271.

This paper is a summary of a number of articles appearing in other journals, and is indirectly of interest to endocrinologists. The research was primarily undertaken to determine whether it is necessary to assume the existence of a combined sugar of colloidal form in the blood in order to explain the complete impermeability of the normal kidney to glucose. By means of perfusion experiments with frogs in which the renal portal system was tied off so that only the glomeruli could function, it was found that the glomerular membrane has the power of retaining free glucose. This power is governed by the influence of the chemical composition of the perfusion fluid upon the glomerular epithelium. When Ringer's solution of the usual composition containing 1% glucose is used then 0.3% is excreted and 0.7% is retained. In the perfusion liquid the quantities of potassium and calcium can be altered with respect to each other in such a way that the retentive power need not be changed, and the potassium can be replaced by radium or uranium, the amount required being proportional to their radioactivity rather than to their atomic weights. However, when the concentration of the sodium bicarbonate in the Ringer's solution is raised from 0.2% to 0.285%, the quantity which is present in frog's serum, all the glucose in the perfusion fluid is retained, the artificial urine being sugar-free. It is, therefore, unnecessary to postulate a combined sugar in the blood.

However, when the amount of glucose in the perfusing fluid is increased some of the sugar is not retained, and the greater the degree of hyperglycemia produced the stronger the permeability becomes. Once the kidney has become permeable, it cannot again be rendered impermeable by reducing the amount of sugar, at least not during the several hours taken by the experiment.

The retention of glucose is not due to the size of the molecule since sucrose, maltose, lactose and raffinose are not retained. It is probably due to the configuration of the molecule since the isomeric fructose, the stereo-isomeric mannose and galactose and even the laevo-rotatory glucose pass through the glomerular membrane. If a mixture of glucose and another sugar is present the glucose only is retained.

The following provisional hypothesis is submitted. As long as the concentration of sodium bicarbonate in the blood plasma is normal, even a moderate hyperglycemia will cause no glycosuria. If, however, the sodium bicarbonate concentration is diminished, the glomerular epithelium becomes sen-

sitive to the proportions of calcium and potassium in the blood plasma. A deficiency in the potassium must be met artificially, but the excretion of sugar can be prevented also to a large extent by increasing the concentration of $NaHCO_3$.—L. G. K.

**(PANCREAS). Notes on two cases of diabetes melltius.** Horsburgh (P.) and Nicol (W. D.), St. Barth. Hosp. J. (Lond.), 1917-18, **25,** 43-45.

A detailed clinical report of two cases of diabetes mellitus, the first of whom, a young boy, responded favorably at first to the hunger and vegetable diet, but failed a fortnight later and improved on having 25 gms. of carbohydrate added to the diet. The second case had 40 grams added suddenly to the diet and showed a tolerance for the same.—F. S. H.

**(PANCREAS) Diabetes, The fasting treatment of—.** Hume (John), Brit. Med. J. (Lond.), 1916 (ii), 160.

See previous abstract.—L. G. K.

**(PANCREAS) Pancreatic diabetes. (Le diabete pancreatique).** Labbé (M.), Ann. de Med. (Paris), 1919, **6,** 204-217.

After giving an historical resume of the evolution of the ideas concerning pancreatic diabetes, Labbé presents six cases with the clinical picture of a double syndrome: insufficiency of of the glyco-regulating mechanism through the abolition of the internal secretion of the pancreas, and digestive insufficiency through suppression of the external secretion. The glyco-regulative mechanism presents various degrees of disturbance ranging from a small and passing glycosuria to a complete and continuous glycosuria accompanied by hyperglycemia, polydypsia, polyuria and other symptoms. In the most typical cases there frequently occurs protein denutrition and acidosis. The author considers that the moderate cases without a negative nitrogen balance can be regulated by dietary regime. The digestive syndrome is characterized chiefly by the type of stools voided; these are abundant, fatty, soft and have a butyric odor. Opotherapy with pancreatic products has proven beneficial in Labbé's hands in some cases of the digestive type, but not in all.—F. S. H.

**(PANCREAS) Gas metabolism in diabetes (Gaswechsel beim Diabetes.)** Löffler. Ztschr. f. klin. Med. (Berlin), 1919, **87,** 309.

In not too serious cases of diabetes the effect of the administration of a dose of casein on the respiratory quotient is

just the same as in normal individuals. If in these cases a dose of glucose is given, about as high as the tolerance for carbohydrates, no influence on the respiratory quotient is observed. A second dose of glucose raises the excretion of $CO_2$, but less than would be expected, theoretically. Probably the first dose of glucose fills the glycogen depots. The author concludes that in diabetes there are only quantitative changes in carbohydrate metabolism.—J. K.

**(PANCREAS) The cause of the increased heat production following pancreatectomy in the dog.** Murlin (J. R.), Am. J. Physiol. (Balt.), 1917, **42**, 584-585.

In three experiments on dogs the heat production was determined before and after pancreatectomy; and immediately following each respiration blood was drawn and examined for blood fat. In one case, also, the $CO_2$ carrying power of the whole blood was determined by the Haldane method. Thus it was possible to compare the heat production with the intensity of the protein metabolism (N output in urine), with the concentration of blood fat and with the actual acidosis.

Two dogs were fed before and after pancreatectomy and on the second day the heat production rose 31 and 42 per cent respectively. In a third dog which fasted throughout it rose only 7 per cent, and the increased protein metabolism alone was sufficient to account for the heat production, but not in the dogs that were fed.

In none of these cases did the maximum heat production coincide with the maximum concentration of blood fat, while normally after an injection or meal of fat the increased heat production runs parallel to the blood fat concentration. Since the $CO_2$ carrying capacity of the blood rose after pancreatectomy in the one case studied, acidosis was not considered to be the cause. Nor could any combination of the protein and fat factors be made to account for it in the two fed animals.

—L. G. K.

**(PANCREAS) Blood sugar in diabetes (Blutzuckeruntersuchungen bei Diabetes Mellitus).** Roth (N.), Berl. klin. Wchnschr., 1918, **55**, 589-592.

The blood sugar rises after meals in the early stages of diabetes, but in later stages falls; it is thus no parallel to the glycosuria.—Chem. Abst., **13**, 2399.

**(PANCREAS) The control of acidosis in the treatment of diabetes.** Stillman (E.), Arch. Int. Med. (Chgo.), 1919, **24**, 445-457.

A description of the methods employed at the hospital of the Rockefeller Institute in the detection and prevention of acidosis in diabetic patients. Typical cases are discussed.
—H. W.

**(PANCREAS) Diabetes mellitus, The etiology of—and the diet and condition of life during the war.** Williamson (R. T.), Brit. Med. J. (Lond.), 1918 (i), 139-141.

The histories of 300 cases of diabetes show the following as predisposing causes: (1) prolonged great excess of sugar, sweet food or sweet drinks (alone or combined with other predisposing causes) in 31 per cent; (2) prolonged and intense mental anxiety, worry, overstrain or sudden mental shock (alone or combined with other predisposing causes) in 40 per cent; (3) family history of diabetes (alone or combined) in 25 per cent. No definite predisposing factor was discovered in 19 per cent. In the author's opinion war time food restrictions should lessen the number of cases caused by an excessively sweet diet, while worry and shock would become greater predisposing factors.—L. G. K.

**(PARATHYROIDS) Chondrodystrophie.** Dietrich, Münch. med. Wchnschr., 1919, **66**, 945.

The author found at the post-mortem examination of a chondrodystrophic dwarf of 35 years a hypoplasia of the parathyroids.—J. K.

**PARATHYROIDS, Tetany and the functions of the—.** Paton (D. N.) and Findlay (L.), Brit. Med. J. (Lond.), 1917, (i), 575-577.

Data published elsewhere. See Endocrin., 1917, **1**, 476-480.
—L. G. K.

**(PARATHYROIDS) On glandulae parathyroidea.** Vermulen (H. A.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1919, **63** (II), 1448.

An anatomical description of the parathyroid in different animals. See also Endocrinology, **1**, 333.—J. K.

**PITUITRIN in labor.** Agnew (A. P.), Brit. Med. J. (Lond.), 1916 (ii), 871.

Advocates the use of pituitrin to hasten the late first stage of labor. The pains are more severe but of shorter duration following its use.—L. G. K.

**(PITUITRIN) Sieben Jahre, etc.** Hofbauer, Monatschr. f. Geburtsh. u. Gynäk. (Berlin), 1918, 325.

Correction Endocrin. **3,** 402: For "Holfauer" read "Hofbauer."

**(PINEAL) On the pineal region in human embryos.** Warren (J.), Anat. Rec. (Phila.), 1917, **11,** 428. (Abstract).

A description of the primary arches in the roof of the forebrain of human embryos of 10 mm. and 15 mm., the parapHysis in embryos of 15 mm. to 44 mm. and the post-velar arch in embryos of 23 mm. to 44 mm. Full paper published later. See Endocrinol. 1918, **2,** 67.—E. R. H.

**POLYGLANDULAR disease, Case of —.** Climenko (H.), J. Nerv. & Ment. Dis. (N. Y.), 1918, **47,** 276.

Report of a case showing menstrual disorder, rapid gain of weight followed by loss, polyuria, weakness and mental derangement in which treatment had produced no change.

—A. R. T.

**(REPRODUCTION) Yellow pigmentation and fecundity.** Palmer (L. S.) and Kempter (H. L.), J. Biol. Chem. (N. Y.), 1919, **39,** 313-331.

The authors have shown in a preceding paper that the natural yellow pigment of fowls is derived from the xanthophyll of the food and that it bears no important relation to growth or to the functions of fecundity and reproduction, at least for one generation. The fading of the yellow pigment from the ear lobes, beak, shanks, etc., of hens during fecundity is due to the fact that fecundity deflects the normal path of excretion of the xanthophyll from these parts of the skin to the egg yolk. This fading as the result of egg production is an index of continued fecundity only, and not of heavy laying.

—V. K. L.

**SCLERODERMA in infants (Sklerodermie im Saüglingsalter).** Kraus (A.), Wiener. klin. Wchnschr., 1919, **32,** 830.

Of no direct endocrine interest.—J. K.

**(SECRETIN) Chemical stimulation of the glands of the mucous membrane of the stomach. I. The influence of organ extracts upon the excretion of the gastric juice. (Über die chemischen Erreger der Magendrüsen. 1. Der Einfluss von Organextrak-**

**ten auf die Sekretion des Magensaftes.)** Tomaszewski (Z.), Arch. f. d. ges Physiol. (Bonn), 1918, **170**, 260.

The experiments reported in this paper do not support Edkin's hypothesis of the existence of a specific substance (gastric secretin) contained in the mucosa of the pylorus and causing gastric secretion. Intravenous injection of pylorus extract, like that of other organ extracts, does not produce gastric secretion; subcutaneous injections of extracts of the mucosa of the pylorus and fundus, of the muscularis of the stomach, of the pancreas and of the small and large intestine all cause outpouring of large amounts of gastric juice. This proves that the substance in question is not only contained in the mucosa of the pylorus but in many other organs also. Since only subcutaneous injection of these extracts is effective, it is likely that the effective substance is produced by chemical reactions occurring in the subcutaneous tissue. Attempts to isolate the effective principle were not successful, but revealed a number of its characteristics.—E. U.

**SEX, The control of—.** Bey (L.), Urol. and Cutan. Rev. (St. Louis), 1918, **22**, 642.

A purely theoretical discussion adding but another theory to the long list of sex-control or determination theories. Not of endocrine importance.—A. R. T.

**(SEX?) Uroleptus mobilis Engelm. II. Renewal of vitality through conjugation.** Calkins (G. M.), J. Exp. Zool. (Phila.), 1919, **29**, 121.

Experiments proving that conjugation in protozoa rejuvenates. The usual isolation culture method was employed; a standard food medium was used throughout, and all series were kept under the same conditions. A single ex-conjugant of Uroleptus mobilis, kept from conjugating and from endomixis, goes through approximately 300 generations by divisions, the division rate steadily declining until the protoplasm dies from old age in from seven to nine months. Closely related individuals from such a series will conjugate. Such ex-conjugants invariably give an optimum division rate regardless of the vitality of the parent race at the times of conjugation. The first sixty-day period of all ex-conjugants shows a uniform vitality measured by approximately 17.4 divisions in ten days. If vitality of the parent series is high (e.g. 15 divisions in 10 days) the increase of vitality in the filial series is low (2.4). If vitality of the parent series is low (e.g. 0.2 division in 10 days) the increase of vitality is high

(e.g. J series ex-conjugant from A311 showed an increase in vitality 17.6 divisions in 10 days). Fourteen such series were studied, the conjugations giving rise to them occurring in all phases of vitality of parent series. In all cases the results were the same—high initial vitality, declining division rate, and ultimate death. A sexual reorganization (parthenogenesis or "endomixis") occurs during encystment. Individuals recovered from cysts have the same high rate of division and length of life as individuals after conjugation. Parthenogenesis, therefore, as well as conjugation, rejuvenates. (Author's abstract.)

**SEX, Studies on—in the hermaphrodite mollusc Crepidula plana. III. Transference of the male producing stimulus through sea water.** Gould (H. M.), J. Exp. Zool. (Phila.), 1919, **29**, 113.

The gastropod mollusc, Crepidula plana, passes through a male phase, a transitional phase and a female phase during its life. The male phase is unstable and occurs only as the result of a stimulus furnished by an individual of the same species larger than the one stimulated. Complete isolation of small sexually undeveloped specimens over long periods shows that no development of male characters takes place under such conditions further than the formation of a few spermatogonia. In time female characters appear. Small sexually undeveloped individuals confined at fixed distances of from 4 to 7 mm. from large females where contact is prevented will in the majority of cases develop male characters of various degrees of maturity. Fewer and less well-developed males are produced under such conditions than when the small animals are nearer the source of stimulus. Large individuals of Crepidula fornicata, a species related to Crepidula plana, have not been found to induce male development in small Crepidula plana except in a few doubtful cases. The stimulus to male development acts in such a manner as to indicate that it is a substance given off from the bodies of the large Crepidula plana diffusible through sea water, but very unstable. (Author's abstract.)

**(SEX) Studies on inbreeding. IV. A further study of the effects of inbreeding on the growth and variability of the body weight of the albino rat.** King (H. D.), J. Exp. Zool. (Phila.), 1919, **29**, 71.

The data given show that the growth and variability of the body weights of over 600 albino rats along in the sixteenth to the twenty-fifth generations of the strain inbred brother and

sister from the same litter only. The chief points of interest are as follows: 1. Continued inbreeding does not produce any deterioration in the original albino stock as regards rate and extent of growth and body weight, and neither has it altered the form of the growth graphs for the two sexes. 2. Normal body weight relations of the sexes have not been changed by twenty-five generations of inbreeding. 3. The variability of the body weights of these animals is relatively high at all age periods, and did not decrease as inbreeding advanced. 4. A comparison of the variability of the body weights in different series of stock albinos with that for inbred rats indicates that the increased variability in the inbred animals was due to an environmental and nutritive action, not to inbreeding. (Author's abstract.)

**(SYMPATHETIC N. S.) The irritable heart in general practice. A comparison between it and the irritable heart of soldiers.** Neuhof (S.), Arch. Int. Med. (Chgo.), 1919, **24**, 51-64.

The irritable heart as observed in general practice is similar to that found in soldiers save for the fact that vasomotor symptoms are more pronounced in the former. The etiological factors are similar, but because of severe training and war conditions, dormant and latent neuroses are more readily evoked in the soldier. Hence, the cardiac syndrome is more violent and lasts longer. Infection is a factor only in so far as it induces and produces nerve or muscular fatigue and psychasthenia. No pathologic changes occur in the cardiovascular system. The fundamental cause of the cardiac neurosis with its various manifestations, appears to be due to hyperexcitation of the sympathetic nervous system. Such cases are best treated with mixed bromides and suprarenal gland extracts. The latter seems to stabilize and decrease vasomotor instability by its action on the vasomotor centers, thus counteracting the cause of many of the symptoms.—H. W.

**TESTES, A study of the seasonal changes in avian—.** Watson (Alex.), J. Physiol. (Lond.), 1919, **53**, 86.

Histological. The interstitial cells show their most marked development in the non-oestrus period, and decrease in number as spermatogenesis advances.—T. C. B.

**TESTES, A case of—in a "girl."** Cooke (G.), and Smuts (Ph. A.), West London M. J., 1918, **23**, 21-24.

A description with pictures of an individual presenting the normal secondary sexual characteristics of the female, as well as a clitoris and partial vaginal chamber, but devoid of uterus. She possessed two oval bodies in the ingunial region which, on removal by surgical interference, were found to be immature testes.—F. S. H.

**(TESTIS) Detection of protective enzymes in very small quantities of serum—micro-Abderhalden reaction.** Pregl (Fritz) and de Crinis (Max), Fermentforschung, 1917, **2,** 58-73.

The authors describe a technique whereby Abderhalden reactions can be determined with 2-3 cc. of serum. They investigated among other things the effect of serum from cases of dementia precox upon dried testicular material. The reaction was positive. Numerous other data on technique, etc., included in the article will be of interest to those undertaking studies of the Abderhalden reaction. (Further details in Chem. Abst., **13,** 3230.)—R. G. H.

**(TESTES) The form of the tubules in the embryonal testicle of the mouse (Over den vorom van de zaadkanaaltjes in den embryonalen testikel van de muis).** de Ruiter (H. T.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1919, **63** (II), 1503.

Of no endocrine interest.—J. K.

**(TESTES) Muskelatrophie.** Schmidt. Berl. klin. Wchnschr., 1919, **56,** 667.

A case of dystrophia musculosum of the masseter and the temporal muscle and of myotonia (so-called atrophic myotonia), with formation of cataract and atrophy of the testicle. —J. K.

**(TETANY) Endemic rickets in adults (Endemisches Auftreten von Spätrachitis).** Bittorf (A.), Berliner klin. Wchnschr., 1919, **56,** 652.

In Breslau many cases of rachitis were observed in men of 15-18 years. In all cases symptoms of tetany were seen. In one case there was a goitre with slight symptoms of Graves' disease. Treatment consists in rest, good and abundant feeding and calcium preparations.—J. K.

**(TETANY) Endemic disease of the bones (Endemisch auftretende Erkrankungen des Knochensystems).** Fromme, Berl. klin Wchnschr., 1919, **56,** 667.

In Göttingen many cases of a rickets-like disease were observed in male individuals of 11-18 years. The bones contained less calcium than normal. In many cases symptoms of latent tetany were observed. The cause is probably an abnormal function of the endocrine organs, caused by poor nutrition.
—J. K.

**(TETANY) Ueber sensible und sensorische Tetanie.** Curschmann (H.), Münch. med. Wchnschr., 1919, **66**, 983.

The author describes two new symptoms of tetany. One patient had attacks in which "she felt her own body," an abnormal sense perception. Another patient had attacks of spasms in the tongue. During these attacks her taste and her smell were changed: bitter substances tasted sour, etc.—J. K.

**(TETANY) Hemi-tetany and lesions of the cerebrum (Hemitetanie bei Grosshirnlaesion).** Spiegel (E.), Deutsche med. Wchnschr. (Berlin), 1919, **45**, 928.

After removal of a goiter paralysis of the left side was observed, with tetany in the paralyzed muscles. The author thinks that during the operation an embolus caused a disturbance in the function of the right side of the brain.

Perhaps during the operation the parathyroids were partly removed; this would not be enough to cause tetany in a normal muscle, but the lesion of the brain had increased the irritability of the muscles of the left side. Therefore one-sided tetany was seen.—J. K.

**(THYMUS) A review of the recent literature bearing on the function of the thymus gland.** Blatz (W. E.), J. Lab. and Clin. Med. (St. Louis), 1919, **5**, 50-54.

The content is sufficiently indicated in the caption.
—B. T. S.

**(THYMUS, PARATHYROID) Fragile skeleton and blue sclerae (Het. broze skelet en de blauwe sklerae).** Bolten (G. C.), Medisch Weekblad (Amsterdam), 1919, **26**, 289, 301.

This disease is due, according to Bolten, to insufficiency of the thymus and the parathyroids and a beginning hyptonia of the sympathic system. The X-rays show that the bones are poor in calcium. It was reported by Klose, Vogt and Erdheim that thymectomy or parathyroidectomy are followed by fragility of the bones. In experiments on animals after thymectomy symp-

toms of tetany have been reported. Bolten saw in all his cases symptoms of latent tetany. (Recent detailed experiments in Japan and in the United States show that thymectomy causes none of the effects postulated.—Ed.)—J. K.

**THYMUS, A recent thesis upon the biology of the— (A propos d'une thèse récente sur la biologie du thymus).** Dustin (A. P.), Arch. Zool. Exper. et Gen. Notes et Revue (Paris), 1916, **55**, 95-109.

The author reviews briefly a recent article by Salkind on the thymus of mammals, birds, reptiles and amphibians. The author regards the small thymic cells as epithelial in origin. He states that in amphibian larvae on a thymus diet (rich in nucleins) the epithelial pouches of the pharynx that give origin to the thymus become very large, forming large thymus glands which contain a relatively large number of small thymic cells, but not of the other cellular elements, and the reverse is true in starving larvae. Thymus feeding also causes an increase in the number of small thymic cells, and thyroid feeding a destruction of the small thymic cells of adult frogs.

Dustin states that the small thymic cells are the only fundamental, constant, specific elements in the organ, and that all other elements are inconstant and variable, are produced by metaplasia, and are simply episodes in the degeneration of the thymus. It is concluded that the thymus is not a true gland, but is rather the center of nuclein metabolism acting as a reserve for nucleins which are liberated by hormones from other organs such as the liver and pancreas. (The author's conclusion finds some support in the rapid loss of thymic substance in inanition and wasting diseases.)—E. R. H.

**(THYMUS) A few words on the human thymus gland (Quelques mots a propos du thymus humain).** Dustin (A. P.), Ann. et Bull. Soc. Royale Sci. Med. et. Nat. (Bruxelles), 1919, —, 30.

Sections through the thymus glands of individuals who succumbed suddenly to accidents demonstrated that the thymus remains functionally active to a relatively high age. In individuals of 40 years the thymus is still rich in small lymphocytes and consequently in chromatin. In persons who died from diseases of longer duration, typical thymus involution was observed, similar to that in fasting vertebrates. The thymus reacts in a most sensitive way to nutritive disturbances. Dustin also calls attention to the work of Delezenne who recently found that the thymus is among the organs very rich in zinc,

this being closely associated with the nucleolytic ferments. D. thinks that this is another fact supporting his theory, according to which, the thymus plays a very important role in regulating the nuclein metabolism of the body.—E. U.

**THYMUS and THYROID (Thymus et corps thyroide).** Dustin (A. P.) and Zunz (E.), Bull. Soc. R. Sc. Méd. et Nat. Bruxelles, 1919, —, 27-28 (Mch. 3)

The thymus is rarely atrophic in men of 19 to 34 years of age who have succumbed rapidly to war wounds. Large thymuses were found associated with small thyroids and vice versa, which fact seems to indicate that there is a balance between the two organs.—Physiol. Abst., **4,** 339.

**(THYMUS) Infantile eczema and status lymphaticus.** Lindsay (L. M.), Can. Med. Assn. J. (Toronto), 1917, **7,** 135-136.

A case of sudden death in a child suffering from infantile eczema is recorded. At autopsy an abnormally large thymus gland was found. The diagnosis of status lymphaticus was made. The case is presented because of the existence of a difference of opinion as to the cause of sudden death in infants with eczema.—L. G. K.

**(THYMUS) Malignant neoplasms of the thymus gland.** Strauss (S. G.), N. Y. Med. J. (N. Y.), 1919, **110,** 646-648.

The thymus is an endodermal epithelial structure remnants of which surely persist to forty, probably longer. Malignant neoplasms arising from the gland may be divided into sarcomata and carcinomata, and a diagnosis of such may be made in spite of the absence of Hassal corpuscles in the growth. Sarcoma is more common than carcinoma in the young, carcinoma more frequent in the aged.—H. W.

**(THYMUS, THYROID) Operation upon the thymus in Graves' disease (Thymusoperation bei Basedow).** Melchior, Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1061.

When, during operation for Graves' disease, the thymus is removed, exacerbations may just as well be observed as in cases where the thymus is left in its place. Removal of the thymus has sometimes a fatal influence on the symptoms of Graves' disease.—J. K.

**(THYMUS) Studies on the reputed endocrin function of the thymus gland (Albino rat).** Takenouchi (M.), J. Exp. Zool. (Phila.), 1919, **29,** 311.

The serum obtained from rabbits immunized with the thymus substance of the albino rat shows a positive precipitin reaction with thymus extract, but this is not strictly specific. The anti-thymus rabbit serum does not show any positive hemolytic action against rat corpuscles when guinea-pig normal complement or rat normal serum is used as complement. The anti-thymus sera injected into rats do not cause symptoms of "primary antiphylaxis," neither are the rats affected in their growth. No modifications of the viscera were observed. Nearly the same results were observed with anti-testis serum from rabbits injected with rat-testis emulsion. Hemolysin production in rabbits by injection of washed rat blood corpuscles was attempted, but the normal rat serum with its complement cannot activate the hemolysin against the rat corpuscle, owing to the presence of some inhibiting substance. The chicken is not suitable for the production of the hemolysin acting on the rat corpuscles. Our attempt to produce strong anti-thymus serum from the rabbit by the injection of rat thymus failed probably because of anti-body production in the rabbit and because the thymus cells of the rat are protected. We cannot yet admit that any endocrin function of the thymus gland has been established. (Author's abstract.)

**Persistent THYMUS in exopthalmic goitre.** Tebbutt (A. H.), Med. J. Australia (Sydney), 1918, **5**, 430-431.

A report of a case of exitus after removal of the right lobe of the thyroid gland and the finding at autopsy of a persistent thymus. This, however, is not considered to be the cause of death through pressure and cardiac inhibition since the terminal phases did not present a picture leading to such conclusion.—F. S. H.

**(THYMUS?) Clinical notes of a case of myasthenia gravis.** Thomson (J.), Brit. J. Child. Dis. (Lond.), 1919, **16**, 92.

The author gives a good clinical report of this rare condition in children in a girl of 11½ years of age. The child died five and a half months after he had seen her. He does not make any mention of any treatment employed.—M. B. G.

**(THYMUS) Sudden death by acute dilatation of the heart consecutive to excessive strain of a man with an enlarged thymus (Mort subite par dilatation aigue du coeur consécutive au surmenage chez un homme porteur d'un gros thymus).** Tricoire (R.), Bull. Soc. Méd. des Hôp. (Paris), 1919, **43**, 98-100.

A description of a case of sudden death of a young man with an enlarged thymus. Autopsy revealed a greatly dilated heart, and hypertrophied thymus. There were no other lesions.

The author suggests that "hyperthymisation" appears to lead to hypotonicity of the heart muscle whereby conditions of stress acting as secondary causes overwhelm the weakened heart leading to death by acute dilatation.—A. L. T.

**THYROID and HEAT REGULATION (Schilddrüse und Wärmeregulation).** Adler, Berl. klin. Wchnschr., 1919, **56,** 958; Münchner Med. Wchnschr., 1919, **66,** 1039.

When in warm-blooded animals the temperature rises one or two degrees, the excretion of carbonic acid is increased approximately 80-100 per cent; in frogs this is not seen. The author tried to explain this difference. He found that frogs from the Alps have a strongly developed thyroid. If these animals are kept at a high temperature, the thyroid becomes atrophic. Probably in frogs the thyroid has a regulatory function. In mammals the same function may be observed. In bats during hibernation, the colloid in the thyroid disappears and the whole gland shows a largely diminished function. If thyroid extract is injected in a hedge-hog during hibernation, 1½ hours after the injection respiration becomes more frequent; after approximately three hours the animal gets up and runs away. Extracts of other organs have no influence. Only extract of thymus may have some influence. A remarkable symptom in the hedge-hog is also that after the injection of extract of thyroid the temperature rises from about 9° to 34-35° C.

—J. K.

**(THYROID) Radium therapy in hyperthyroidism with observations on the endocrinous system.** Aikins (W. H. B.), Internat. J. Surg. (N. Y.), 1918, **31,** 217-224; Radium (Pittsburg), 1918, **11,** 81-90.

See Endocrin., **2,** 537.

**(THYROID) Development of the thyroid glands of Bufo and their normal relation to metamorphosis.** Allen (B. M.), J. Morph. (Phila.), 1919, **32,** 489.

The accumulation of colloid material of the thyreoid glands of toad tadpoles begins just as the hind limb buds appear. The colloid masses increase in size and number until the forelimbs break through the skin. The accumulation of colloid material is accompanied by a marked increase in the size of the

thyreoid gland, which appears in the main to be a direct result of it. The apparently paradoxical fact that there is a cessation in growth and actual diminution in the size of the thyreoid gland and of the colloid masses at the very time when the process of metamorphosis is most active might in part be explained as the result of a partial drying process due to the emergence of the tadpoles from the water were it not that they do not emerge upon the land until later. The reduction in size is thus under way before this factor can prove effective. It is much more probable that this diminution may be due to the absorption into the blood of an unusually large amount of stored colloid at this time when it would prove most effective. The tail steadily increases in size to a certain point, shows a slight diminution and then quickly disappears. Either the thyreoid secretion does not cause the shrinkage of the tail or it must reach a considerable volume before it is able to accomplish that result. It is certain that limb development in the process of this appearance of the tail follows the accumulation of colloid in the thyreoid glands of Bufo. (Author's abstract.)

It might be noted that anurans decrease in size during metamorphosis more than do their thyreoids, so that despite some actual decrease in the size of the thyreoids at this time there is a relative increase.—E. R. H.

**(THYROID, HYPOPHYSIS) The relation of the pituitary and thyroid glands of Bufo and Rana to iodine and metamorphosis.** Allen (B. M.), Biol. Bull. (Woods Hole), 1919, **36**, 405.

Hypophysis removal in the larval amphibia retards the development of the thyroid glands as was shown by Adler '14. Thyroid removal causes hypertrophy of the pituitary (shown by Hoskins and Hoskins '18, Rogers '18 and Larson '19). The author believes that the thyroid probably plays the rôle of iodine storage and controls its distribution and that it is possible that the pituitary might play the chief rôle in the utilization of iodine by the body, because tadpoles deprived of either the thyroid or pituitary fail to metamorphose on a normal diet but either group and those deprived of both these glands will metamorphose when iodine is administered. (One possible objection to Allen's theory is that larvae deprived of the thyroid can be brought to metamorphosis by the administration of pituitary substance, which is practically free from iodine.)

—E. R. H.

**(THYROID) Hypothyreoidismus, Rachitis und Tetanie.** Bauer (F.), Wiener klin. Wchnschr., 1919, **32**, 929.

A short note on a case with symptoms of myxedema, rickets and tetany.—J. K.

**(THYROID) Basedow's disease and war (La maladie de Basedow et la guerre).** Berard (Leon), Bull. Acad. de Méd. (Paris), 1916, **76**, 428-430.

Berard refers to the frequent occurrence of Basedow's disease among soldiers and also civilians under conditions of special stress. These may develop from a pre-existing goitre of varying size or may appear without any evident pre-existing abnormality. Proper treatment consists of: (1) complete isolation of the patient in such a situation as to induce complete security and comfort; (2) Hydrotherapy; (3) quinine sulphate, 1 gram, and sodium salicylate, 2 grams, given on alternating days. Some good results have been obtained by ingestion of fresh thymus, and by subcutaneous injections of serum of thyroidectomized animals.

If after five to six months of this methodical drug treatment the subject has not properly responded, he is submitted to surgical treatment—the ligation of thyroid vessels, or excision of portions of the glands. As anaesthetic Berard uses ether, with morphine and atropine.—A. L. T.

**(THYROID) Neuroses and hormone therapy. Dysthyroidism as a factor in neuroses. The oculo-cardiac reflex as a control of hormone therapy (Névroses et opothérapie. La dysthyroïdie facteur de névroses. Le réflexe oculo-cardiaque régulateur de l'opothérapie thyroïdienne).** Blanc (Jean), Progres Méd. (Paris), 1917, **32**, 95.

In certain psychoneuroses the author has studied the claim that the oculo-cardiac reflex of Aschner indicates the relative tonicity of the sympathetic as opposed to the parasympathetic nervous system. In hypothyroidism when pressure is made on the eye-ball there is a greater slowing of the heart than normal; on the other hand, in hyperthyroidism the decrease in heart rate is excessive. Occasionally after thyroid medication the result is "negative," i.e. instead of slowing of the heart there occurs acceleration. This was taken to indicate an excessive irritability of the sympathetic system. Blanc begins thyroid medication with doses of 0.002 mg.(!) given alone or with 1 mg. of parathyroid. These doses are given two or three times a day, results being followed or controlled by general clinical appearances and by the reflex of Aschner.—A. L. T.

**(THYROID) The relation of neurocirculatory asthenia to hyperthyroidism as determined by the effects of injection of**

**epinephrin.** Boas (E. P.), Arch. Int. Med. (Chgo.), 1919, **24,** 419-421.

Individuals suffering from neurocirculatory asthenia show a positive epinephrin reaction, as indicated by alterations in the pulse rate, blood pressure and augmentation of nervous phenomena. Some positive reactions are accompanied by precordial pain, vertigo, headache, epigastric distress and nausea. In four cases of palpable thyroid only one gave a positive epinephrin reaction. On the other hand, individuals showing a negative epinephrin reaction may have well defined goitres. Hence, it is impossible to predict from any criteria at present available whether or not any particular case of neurocirculatory asthenia is sensitive to epinephrin.—H. W.

**THYROID gland, Malignant epithelial growths of the—.** Bonn (H. K.) J. Ind. State Med. Assn. (Ft. Wayne), 1919, **12,** 67-69.

Reviews the literature on malignant tumors, discussing the pathological and histological diagnosis, and reports one case of squamous cell carcinoma, three of adeno-carcinoma and one of sarcoma of the thyroid. Bonn concludes that early diagnosis of malignant thyroid growths may be made when a goitre long quiescent suddenly increases in size, accompanied by a change in consistency.—L. F. W.

**(THYROID) Surgical treatment of exophthalmic goitre.** Crile (George W.), Proc. Clin. Congress Am. Col. Surgeons, 1919, Abst., J. Am. M. Assn. (Chgo.), 1919, **73,** 1633. Discussion, Lewis (Dean D.); Mayo (Charles H.)

Of 2,250 thyroidectomies, 50 per cent were subjected to ligations. In 333 cases, ligation was first done, then a thyroidectomy. Among 116 ligations, one death occurred in the stage of dissolution. In the first 100 cases the mortality was 16 per cent. With the use of gas and oxygen anesthesia this was reduced to 2.5 per cent. By the adoption of special management of cases, the mortality has been further reduced to 0.6 per cent. Since the war, special precautions have been added against postoperative hyperthyroidism due to excessive chemical activity and destruction by oxidation. With each degree of rise of temperature this chemical activity is increased 10 per cent. With a temperature of 106 F., metabolism is increased 70 per cent. Another point of importance was the discovery by the British research department that the wound can be left open in statu quo, by the use of a dressing of 1:5,000 flavine. This permits the surgeon to stop at any point at which he considers the patient is not enduring the operation

well. Lobectomy is performed under analgesia, as the inhalation anesthesia interferes with internal respiration in a patient already suffering from suboxidation. Hypersensitiveness is sufficient to destroy the patient. Complete team work is essential to success. The operation is performed by the hospital and not by the surgeon. The differential diagnosis is greatly aided by the Goetsch epinephrin test and basal metabolism determination.

DISCUSSION

Tachycardia without exophthalmos does not differ from ordinary thyreotoxic goitre. Hyperplasia of the thyroid epithelum presents the four classical signs of goitre. Surgeons are likely to want to operate too soon. The exercise of judgment makes all the difference between one surgeon's success and another's lack of it. I have seen patients die after ligation. I have not seen anything that will control that.

—D. D. L.

The Surgeon-General's report showed that 15 per thousand is the rate of goitre in the northern Pacific States. There is almost no goitre in New Hampshire and Vermont. There are perhaps more mistakes in diagnosing exophthalmic goitre than any other condition. The thyroid is not essential to life, but it is synonymous with making life worth living. The cell changes in the thyroid are due to increase of biochemical products by bacteria, coming from different parts of the body and acting on the thyroid. Two-thirds of the cases are simple hyperplastic glands. A second type is caused by areas of degeneration throughout the gland. A hyperplastic gland sometimes goes with myxedema—a sort of burned-out condition. In hyperthyroidism there is a burning of fats, a rapid oxidation, and these people literally destroy their own cells. The thyroid gland bears relation to the elimination of nitrogen. Nitrogen, if retained, leads to tetany. Creatin and creatinin have almost the same chemical constitution as the thyroid secretion. There is, however, no positive determining factor to tell what is the controlling influence in thyroid action. We do not all agree as to methods, but the important point is that the mortality has been brought down.—C. H. M. (Quoted).

**(THYROID) Nervous cretinism.** Crookshank (F. G.), Lancet (Lond.), 1917 (ii), 604-605.

Nervous cretinism was first described by McCarrison as occurring in India. The author describes a number of cases observed by him in English children. In almost every case there is evidence of dysthyreosis in the mother or other members of her family. The earliest manifestations of mild ner-

vous cretinism are generally regarded as tetany and occur towards the end of the second year of life. Sometimes a pale puffiness representing the myxoedematous phase of dysthyreosis is present; this is usually transient. Later there may ensue a stage of weakness, with tottering gait, and a more persistent spasm that passes into a condition not to be distinguished from "congenital spastic diplegia" or "Little's disease" of moderate degree. In the more severe cases mental defect is obvious almost from the first, and the early appearance of spasm with nystagmus leads to the diagnosis of congenital spastic diplegia. All cases of nervous cretinism are found to improve under thyroid medication.—L. G. K.

**The THYROID gland, Local anesthesia in operations upon—.** De Courcy (Joseph L.), Am. J. Surg. (N. Y.), 1919, **33**, 245-248.

De Courcy advises early operation whenever possible on the ground that in skilled hands there is no more danger in removing a simple adenomatous or benign (not exophthalmic) goitre than there is in interval appendicectomy; and benign goitre should be considered as potentially dangerous as a simple appendicitis or a hernia. Preliminary observation and treatment in all cases of exophthalmic goitre with intensive study of the heart, kidneys and blood, are important. If case does not respond to internal medication and rest, arterial ligation should be performed. As a general rule the author does not perform thyroidectomy when the pulse after a moderate amount of exertion exceeds 120 per minute. He believes that a greater risk can be taken when local anesthesia is used than is possible under general narcosis, and that arterial ligation will be less often indicated. Removal of both lobes and isthmus gives the best results in exophthalmic goitre and causes less reaction following operation. Thyroidectomies can be done painlessly and thoroughly under local infiltration.—R. G. H.

**(THYROID) Endemic goitre (Vom endemischen Kropf).** Deist (H.), Schmidt's Jahrbücher (Bonn), 1919, **330**, 1.

A general review of the theories as to the cause of endemic goitre. The author supports the well known theory of Bircher. He believes that it is absolutely necessary that all researches done on goitre in the whole world be international and judged by a central international commission.—J. K.

**(THYROID) A case of Graves' disease (Ein Fall von Morbus Basedowii).** Falta (W.), Wiener klin. Wchnschr., 1919, **32**, 157.

Description of a case with exophthalmos of only one eye. There are 109 of these cases reported in the literature.—J. K.

**THYROID aplasia (Ein Fall von Thyreoaplasie).** Falta (W.), Wiener klin. Wchnschr., 1919, **32**, 157.

A new-born baby suffered with marked constipation. Later there was no growth of the hair. Thyroid treatment had a good effect. During war it was impossible to get thyroid tablets. The child became worse and worse; obstipation reappeared, the psychic development became bad. A piece of a thyroid of a patient with Graves' disease was transplanted without success. As soon as it was possible, thyroid tablets were regularly given. The success was complete.—J. K.

**(THYROID) Myxoedema.** Fischl (R.), Berliner klin. Wchnschr. 1919, **56**, 479.

A case of myxoedema with retarded ossification of the bones of the hands was benefited by the administration of thyroid preparations. A short note.—J. K.

**(THYROID) Paralyse chez une hypothyroïdienne.** Fournier (J. C. M.), Rev. Neurol. (Paris), 1918, **25**, 62-65.

Published elsewhere. See Endocrin., **2**, 536.

**(THYROID) The operative treatment of simple enlargements and tumors of the thyroid gland.** Frankau (C.), Brit. Med. J. (Lond.), 1919 (i), 792, 794.

Operation is rarely necessary in colloid goitre since it yields fairly readily to medical treatment. Surgical treatment should be carried out only when there are definite symptoms or deformity. No palliative treatment gives relief in diffuse adenoma, hence operation is justifiable if the enlargement is marked, even if no symptoms are present. Cysts of the thyroid form the most frequent class operated on, since they may grow to a very large size and dyspnoea is usually present.

A certain amount of detail concerning the surgical technique is included in the paper.—L. G. K.

**(THYROID) Mental symptoms predominate in some cases of myxoedema.** French (H.), Guy's Hosp. Gaz. (Lond.), 1918, **32**, 72-73.

Brief description of two cases of myxedema presenting marked mental disturbances. The first case cleared up on thy-

roid opotherapy and continues normal. The second case was diagnosed as frontal lobe tumor and was trephined, but no tumor was found. Dying of erysipelas, the patient was autopsied and the only abnormality found was that the thyroid gland existed as a trace only, the right lobe being fibrous tissue and all weighing about 0.7 gram. The left lobe weighed still less. The conclusion is that this latter case might have been benefited by thyroid treatment and that myxedema may have mental and cerebral symptoms as its predominant features.

—F. S. H.

**THYROID, Malignant tumor of—.** Graves (S.), Ky. Med. J. (Bowling Green), 1919, **17,** 325.

A case report.—H. W.

**(THYROID) Toxic, non-exophthalmic goitre.** Haggard (William D.), Proc. Southern Med. Assn., J. Am. M. Assn. (Chgo.), 1919, **73,** 1796.

This type of goitre is quite as dangerous, if not more so, than exophthalmic goitre, because the toxin seems to have a selective action on the heart, causing the so-called "goitre heart," thyrotoxic, instead of the mechanical "goitre heart" from pressure. It is more likely to be overlooked on account of the absence of exophthalmos. Many simple adenomas are prone to degenerate and produce toxic symptoms. An atoxic goitre may be of long duration before producing toxic symptoms. There is danger in administering iodin in a case of goitre of long standing. It may set up toxic and sometimes fatal symptoms. Toxic, non-exophthalmic goitre occurs in one out of four goitres that are not hyperplastic. Toxic goitre is not definitely improved by ligation. Operation for toxic goitre is quite as dangerous, if not more so, than in the exophthalmic type, owing to the condition of the patient. In my last series of 100 toxic cases, exclusive of the so-called simple goitre, two deaths occurred in thirty-three operations, and only two deaths in sixty-seven exophthalmic cases.—Quoted.

**(THYROID) Struma apoplectica.** Hering. Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1061.

A very short note on hemorrhage into the thyroid observed in a patient after severe coughing.—J. K.

**THYROID, A case of acute purulent inflammation of the—(Ein Fall von Thyreoiditis acuta suppurativa).** Höpfner (H.), Berliner klin. Wchnschr., 1919, **56,** 944.

Description of a not very important case of an abscess in the thyroid, cured by incision.—J. K.

**(THYROID) Growth and development of amphibia as affected by thyroidectomy.** Hoskins (E. R.) and Hoskins (M. M.) J. Exp. Zool. (Phila.), 1919, **29,** 1.

The thyroid anlage was removed from very young embryos of Amblystoma punctatum and Rana sylvatica. The technique is described. In some larvae the gland regenerated. When correctly performed, this operation will inhibit metamorphosis more or less indefinitely if the animals are kept on a normal diet. Thyroidless larvae grow more rapidly than the controls and ultimately become two to three times as large. Inhibition of metamorphosis in these animals is attributed to a defective metabolism, especially of calcium, since the earliest and most striking effects were noted in the skeleton which calcified and ossified less completely than normal. Other characteristics of thyroidless amphibians are: retention of the larval form, and the ability to regenerate lost parts; the brain develops slowly; the hypophysis hypertrophies; the thymus persists and becomes relatively large; the epitheleoid (parathyroid) bodies and kidneys become relatively large; the spleen is not affected; the internal gills persist; the lungs develop and become functional; the intestine retains its larval character; the ovaries differentiate and form large oöcytes which do not completely maturate; the testes develop to maturity, producing spermatozoa which escape through the kidneys. The changes in the body and organs of normal larvae during metamorphosis are described and also the histology of the endocrine glands and organs of normal and thyroidless animals.—Author's abstract.

**(THYROID) An experimental and clinical study of the isolated thyroid hormone.** Janney (Nelson W.), Dental Cosmos, (Phila.), 1918, **60,** 133-139.

An address covering the work of the speaker and his coworkers on the subject. The data were previously reported in the following articles:

The anabolic action of the thyroid gland. Proc. Am. Soc. Biol. Chem. (N. Y.), 1916, **11,** 6.

An experimental and clinical study of the isolated thyroid hormone. Sec. on Ped., N. Y. Acad. of Med., 1917, April. See Med. Rec. (N. Y.), 1917, **91,** 1161.

hormone. Apr. Dental Cosmos (Phila.), 1918, **60,** 133-139

An experimental and clinical study of the isolated thyroid

The blood sugar in thyroid and other endocrine diseases Arch. Int. Med. (Chgo.), 1918, **22,** 160.

The influence of thyroidectomy and thyroid diseases on protein metabolites. Ibid, 1918, **22,** 174.

In addition experimental data were mentioned which militate against acceptance of the well known theory of endocrine function of Falta, Eppinger and Rudinger of the Viennese school. Probably the endocrine glands have (1) a general somatic action on the building and replacement of the protein molecule and (2) a specific action as exemplified by development of the secondary sexual characteristics at the time of functioning of the sex glands.

**(THYROID) Arhythmias in Graves' disease (Arhytmien beim Morbus Basedowii).** Huber, Ztschr. f. klin. Med. (Berlin), 1919, **87,** 465.

Very often in Graves' disease, extrasystoles may be observed. They are nearly always seen after injection of adrenalin. Also tachycardia of the sinus and arhythmia perpetua may be observed. Digitalis has a good influence.—J. K.

**(THYROID AUTONOMIC N. S.) Voluminous goitre, compression of trachea and sympathetics. Exaggeration of the oculocardiac reflex [Goitre volumineux, compression trachéale et sympathique (Syndrome de Claude Bernard-Horner). Exagération du réflexe oculo-cardiaque].** Jacob (P.) and Labeaume, Bull. Soc. Méd. des Hôp. (Paris), 1919, **43,** 446.

On the side of excessive pressure, ocular signs indicate sympathetic nerve trauma or paralysis, as shown by exophthalmos, miosis and narrowing of the palpebral fissure. Aschner's eyeball-heart reflex appeared more prominent on the injured than on the normal side, producing a slowing of the heart from 88 to 52, while the slowing on the uninjured side was from 88 to 72. This was taken to indicate that the sympathetic nerve injury on the left side upset the balance between the sympathetic and vagus in such a way as to leave the vagal effects predominant.—A. L. T.

**(THYROID) Symptoms of hyperthyroidism observed in exhausted soldiers.** Johnson (W.), Brit. Med. J. (Lond.), 1919 (i), 335-337.

Observations were made on 50 soldiers who left the firing line complaining of weakness, uncontrollable nervousness, throbbing headaches, dizziness, palpitation and precordial pains, more especially on exertion. Occasionally digestive dis-

comfort and diarrhoea or frequency of micturition were complained of. Sleep was irregular and easily disturbed. Dreams, in which the patient would wake up in a profuse perspiration, were common.

On examination these patients appeared pale, looked ill and were exhausted. The mental state was usually one of subdued excitement. More or less prominence of the eyes was exhibited by all the cases. Tremor was a constant phenomenon. Other signs of "hyperthyroidism" were also generally present.

It was found that after a rest in bed (with full diet, suitable tonics and occasionally Dover's powder at night) the condition of all the patients rapidly improved in ten or twelve days. The exophthalmos greatly decreased or disappeared. The pulse remained rapid and excitable, and the general subjective symptoms always appeared to be within call if the patient experienced any excitement. These cases then merged into the group labelled "neurasthenia," and were indistinguishable from them.

The author advances the following hypothesis.

1. That a large number of so-called psychoneuroses are cases in which the symptoms are due to a state of disordered internal secretion, the result largely of emotional exhaustion, and, to a less degree, of physical exhaustion. 2. That many cases which are later diagnosed irritable heart, "D. A. H." soldier's heart and neurasthenia are really cases of this class, and that possibly many have passed through a slight state of exophthalmos without its importance being realized.

The phrase "exhaustion syndrome" is suggested as a suitable term to apply to this group of symptoms, and exhaustion is declared to be the active etiological factor in all these cases of breakdown.—L. G. K.

**(THYROID) Pit in the thorax in a child with Graves' disease. (Dellenförmige Einziehung der Herzspitse bei Basedow).** Just, Deutsche med. Wchnschr. (Berlin), 1919, **45**, 1119.

Demonstration of a girl of 9 with Graves' disease and a pit in the thorax at the location of the cardiac apex. Of no special endocrine interest.—J. K.

**(THYROID) Local anesthesia for operations for goitre.** Keller (A. A.) New Orleans M. & S. J., 1919, **71**, 305-310.

The author discusses the dangers of general anesthesia. He believes that local anesthesia offers greater safety and is particularly suited to thyroidectomy. He has employed novocain and aposthesine with good results, and observes that there

is less post-operative pain and a shorter convalescence after local than after general anesthesia. He reports forty-five operations on the thyroid under local anesthesia.—L. F. W.

**(THYROID) Isolation of the iodine compound which occurs in the thyroid (first paper).** Kendall (E. C.), J. Biol. Chem. (N. Y.), 1919, **39**, 125-149.

The original must be consulted for details in isolating the active principle "thyroxin" in quantity from the glands. Thyroxin is shown to be 4, 5, 6—trihydro—4, 5, 6, triiodo—2 oxy, betaindole-propionic acid and exists in three forms: (1) the keto form with the carbonyl group adjacent to the imino; (2) a tautomeric enol form of this, with an alpha hydroxyl group and double bonded nitrogen, with no hydrogen attached to the imino, and (3) a form in which there is an open ring structure, the elements of water entering between the imino and the carbonyl with the formation of an amino and carboxyl group.

Five chemical reactions are involved in controlling the conditions of its isolation. (1) Iodine breaks off from the acetyl derivative when an acid suspension is neutralized by NaOH. Temperature greatly influences this reaction. (2) Pure thyroxin is easily reduced, yielding free iodine, when hydrolysis is carried on in metallic containers. (3) $CO_2$ causes two distinct reactions. It precipitates thyroxin from its impurities and, by forming the monometallic derivative form from the dimetallic, produces an optimum condition for the closing of the indole ring. (4) Increase in temperature during $CO_2$ treatment results in liberation of free iodine. (5) Glands vary in their thyroxin content, the yield being 400-500% higher in summer than in winter. Deamination and decarboxylation are believed to be the cause of the loss in therapeutic power of desiccated glands. This loss may be brought about by bacteria without change in the iodine content.—V. K. L.

**(THYROID) Survey of thyroid enlargement among students of the Puyallup Indian School.** Kerr (W. T.), Northwest Med. (Seattle), 1919, **18**, 110-112.

Of 310 Indian students representing 43 tribes from six states and Alaska, 10.6 per cent showed definite enlargement of the thyroid. The survey shows that in full-blooded Indians the incidence of goitre is very low as compared with part blood or the pure Caucasian race.—H. L.

**(THYROID) A preliminary survey of the thyroid gland among two thousand, one hundred and eighty-two recruits at Camp Lewis, Washington.** Kerr (W. J.), Arch. Int. Med. (Chgo.), 1919, **24,** 347-358.

Study of recruits from eleven northwestern states. Incidence of simple goitre was found to be highest in Washington and Oregon and lowest in California and Nevada. Endemic goitre was found largely confined to Pacific Northwest. Exophthalmic goitre was rarely seen, subjects having this condition being rejected by local boards. Twenty-one per cent of all troops showed definite enlargement of the thyroid gland, of which twenty-seven per cent were rather large. Goitres had been noticed in other members of the family, especially the females. Tremor and tachycardia were occasionally noted. No definite conclusions as regards etiology could be drawn.

—B. T. S.

**THYROID, Influence of extract of—on certain secondary sex characters in the Triton (Influence de l'extrait de thyroïde sur certaines caractères sexuels secondaires des Tritons).** Kollmann (Max), C. R. Soc. de Biol. (Paris), 1919, **82,** 793.

Male tritons when in full sexual activity possess a dorsal crest and large nictatory membrane. These secondary sex characters disappear in the intervals between sexual periods. This recalls the regression of the caudal membranes in tadpoles, which is the first external manifestation of metamorphosis. A group of Molge vulgaris were treated with injections of thyroid extract. The results showed an opposite effect to that expected. Instead of accelerating the disappearance of the crest and membranes, thyroid extract seems to favor their permanence, even after the close of the period of reproduction.

—T. C. B.

**(THYROID) The influence of thyroidin on normal metabolism.** Krogh (Marie), Ugeskr. f. Laeger (Copenhagen), 1916, **72,** 2237-2341.

Correction of reference in Endocrin. **2,** 73, 200.

**(THYROID) Diarrhea in Graves' disease (Durchfälle bei Basedowscher Krankheit).** Koslowsky, Deutsche med. Wchnschr. (Berlin), 1919, **45,** 1219.

The author observed two cases in which diarrhea was the first symptom of Graves' disease. The other symptoms were not very distinct. Treatment with ovary tablets had a good influence on the diarrhea.—J. K.

**(THYROID) Some details of the acceleration of metamorphosis in Anura under the influence of thyroid extract (Quelques précisions sur l'accélération de la métamorphose des Bactracien Anoures sous l'influence de l'extrait de thyroïde).** Kollmann (Max), C. R. Soc. de Biol. (Paris), 1919, **82**, 1009.

Having shown that simply adding thyroid extract to the water produces the same effect as feeding thyroid, the author points out that aside from other factors it is necessary to consider the age of the tadpoles and their state of nourishment. The desirability of the maintenance of a constant temperature is emphasized, and the stage of development of the posterior extremities is taken as a criterion of age.

A large number of tadpoles was selected, as nearly alike as possible, and was then divided into eight lots. Lot 1 had no visible traces of the posterior extremities; lot 2 with whitish buds indicating the posterior extremities; lot 3, posterior extremities visible but very small; lot 4, legs longer, but straight; lot 5, like the preceding, but longer legs; lot 6, legs flexed in the adult position; lot 7, like the preceding, but the body commencing to take the adult form; lot 8, the anterior extremities present. Each lot was divided into two groups; one group was kept in ordinary water, the other had added 2 cc. extract of thyroid for each 100 cc. water.

Under these conditions the extract seems to exert no effect on groups 1, 2, 3 or 4, except in rare individual cases in lot 4, due to the fact that specimens at the identical stage of development cannot be rigorously selected. In lots 5 and 6 it is the rule to have metamorphosis rapidly produced in the "thyroidized" animals, while it is exceptional in the controls. The other lots remain uninfluenced by the thyroid extract.

In regard to nourishment (giving food in addition to thyroid extract), alimentation simply furnishes the material necessary to attain a condition where the animal becomes sensitive to the action of the extract.

Kahn's assertion that the left anterior extremity appears before the right, is not confirmed.—T. C. B.

**(THYROID) Demonstration von Kretinen.** Lange, Münch. med. Wchnschr., 1919, **66**, 945.

The author demonstrated at a medical meeting some cretins treated with thyroid with very little success.

Probably the patients were too old when treatment began; such patients ought to be treated at as early an age as possible. In countries where cretinism is frequent, popular lectures ought to be given to teach the public that treatment must begin when the first symptoms are observed.—J. K.

**(THYROID) The little signs of thyroid disturbance.** Leiner (Joshua H.), Med. Rec. (N. Y.), 1919, **96,** 99-101.

The author calls attention to the "little signs" of thyroid disturbances, believing that numberless cases are unrecognized that might be benefited by early recognition and judicious therapy. Most physicians diagnose correctly outspoken syndromes such as Graves' disease, myxedema, cretinism, but neglect the mild incipient modifications. He cites a few illustrative examples.—H. L.

**(THYROID) Suppurative thyroiditis due to the bacillus paratyphosis A (Thyroïdite suppurée a bacille paratyphique A).** Lemierre (A.) and Taberlet, Bull. et Mem. Soc. Méd. des Hôp. (Paris), 1919, **43,** 513.

A case report of a suppurative thyroiditis occurring in the course of paratyphoid fever.—A. L. T.

**(THYROID) Making the cure of goitre safe.** Levy (Louis), New Orleans M. & S. J., 1919, **72,** 170.

The author emphasizes the importance of careful preliminary treatment for exophthalmic goitre before operation in any case. To prevent shock he uses local or nitrous oxid anesthesia and, following the operation, gives enough morphine to keep the patient quiet, even though the respirations go down to 10-12 per minute. This morphine treatment is usually continued for three days.—L. F. W.

**THYROID, Effect of extract of, on tadpoles.** Lim (R. K. S.) J. Physiol. (Lond.), 1919, **53,** Proc. xxvi.

Precocious metamorphosis as described by Gudernatsch was observed. Microscopic sections show concomitant changes in the viscera, and a remarkable number of mitoses, indicating rapid cell proliferation.—T. C. B.

**Preliminary THYROID operations.** Link (G.), J. Ind. State M. Assn. (Ft. Wayne), 1919, **12,** 64-66.

The author believes that better results follow thyroidectomy when it is preceded by ligation of one or more arteries or by the injection of boiling water. He observes that increased mortality is often due to neglect of this measure.
—L. F. W.

**(THYROID) The use of laboratory methods in the diagnosis of early hyperthyroidism.** Lueders (C. W.), Arch. Int. Med. (Chgo.), 1919, **24,** 432-444.

A study was made to discover a means of differentiating early or borderline hyperthyroidism from functional cardiac disorder. The tests used were sugar tolerance, epinephrin test, nitrogen loss and test for acidosis.

The results showed that the laboratory affords a most reliable aid toward the recognition of early hpyerthyroidism. The sugar tolerance test is an important aid in detection of borderline cases. Epinephrin tests did not prove diagnostic of hyperthyroidism. Tests for nitrogen loss and acidosis seemed suggestive aids. Also creatinuria determinations in conjunction with other tests were of value.—B. T. S.

**(THYROID) Some points in the surgical treatment of goitre.** Mackenty (J. E.), Laryngoscope (St. Louis), 1917, **27,** 912-914; Tr. Am. Laryngol. Assn. (N. Y.), 1917, **39,** 215-227.

Advises operative measures as the surest cure of goitre and thinks that the rhinolaryngologist should do neck surgery. —H. W.

**(THYROID) The basal metabolism in hypothyroidism.** Means (J. H.) and Aub (J. C.), Arch. Int. Med. (Chgo.), 1919, **24,** 404-418.

Determinations of basal metabolism in untreated cases of myxedema showed definite reduction below that of normal individuals. Studies on a cretin and a case of cachexia strumipriva showed the same. Thyroid therapy brought the basal metabolism up to normal. Basal metabolic determinations form a convenient method of governing the dosage of thyroid preparations in hypothyroidism and may be of value in diagnosis. —B. T. S.

**(THYROID) A note on the question of the secretory function of the sympathetic innervation to the thyroid gland.** Mills (C. A.), Am. J. Physiol. (Balt.), 1919, **50,** 174.

The evidence regarding the innervation of the thyroid being conflicting, the object of the experiments was to determine whether the thyroid could be stimulated to greater activity by the use of cocaine according to the method of Froelich and Loewi. Daily injections of 10 mgm. cocaine per kilo, body weight, were given over a period of days and the thyroids were examined histologically for evidence of hyperactivity. No such

evidence could be observed, and the writer considers this an indication of a lack of secretory function of the sympathetic fibres to the gland.—T. C. B.

**(THYROID) Radium.** Mowers (S. W.), Northwest Med. (Seattle), 1919, **18,** 153-156.

In mentioning the many therapeutic indications for radium, the author states that it is very useful in exophthalmic goitre. The majority of the cases are clinically cured and a very large percentage have an actual decrease in the size of the goitre. Others have reported similar success, but further confirmation and longer observation is necessary.—H. L.

**(THYROID) Ligation of the vessels in toxic goitre.** Noble (T. B.), J. Ind. State M. Assn. (Ft. Wayne), 1919, **12,** 230.

Noble urges an early diagnosis of the mild forms of toxic goitre, and prompt surgical interference if the best results are to be obtained. Formerly the condition of the patient was determined by the intensity of the four cardinal symptoms. At the present time it is possible to determine the metabolism rate and thus place the patient on a definite scale of toxicity, selecting the treatment best suited to his needs. Ligation should be reserved for the severe forms of goitre when the life of the patient would be jeopardized by a lobectomy. In the average case lobectomy should never be preceded by a ligation.

—L. F. W.

**(THYROID) The toxic element in goitre.** Pern (S.), Med. J. Australia (Sydney), 1918, **5,** 276-278.

A report of twenty-three cases purporting to substantiate the author's opinion that the cause of goitre lies in a defensive reaction of the thyroid accompanied by hypertrophy due to toxins engendered in the system from infectious processes largely in the teeth and tonsils.—F. S. H.

**(THYROID) The blood picture in exophthalmic goitre.** Plummer (H. S.), Collected Papers of the Mayo Clinic (Rochester, Minn.), 1918, **10,** 359.

This paper is based on the study of the blood counts in 578 patients with exophthalmic goitre. The hemoglobin, erythrocytes, and the total leukocytes are all within normal limits. There is, however, both a relative and an absolute mononucleosis, together with a percentage decrease in the polymorphonuclear neutrophiles. The eosinophiles are slightly under the

normal average. Although some writers still maintain that anemia of the chlorotic type is a characteristic of this disease, this is neither borne out by the author's findings nor those published by Kocher. The author concludes that there is much to indicate that the changes in the leukocyte formula are owing to two more or less independent variables. One which causes a lymphocytosis and another which influences the neutrophilic count. The first may be found in a hyperplasia of the lymphoid tissues, and the second in a fluctuating abnormal distribution of the neutrophiles in the vascular tree.

—J. F.

**(THYROID) Ueber Volumen pulmonis diminutum.** Pollitzer (H.), Münchener med. Wchnschr., 1919, **66,** 1103.

In diseases with chronic contraction of the blood vessels in the lung the volume of the lungs may seem diminished. When the left lung diminishes in volume, it gives the impression that the heart is dilated. This may be observed in chlorosis, chronic malaria and Graves' disease.—J. K.

**(THYROID) Factors for safety and ultimate results in goitre operations.** Potter (C.), J. Missouri M. Assn. (St. Louis), 1917, **14,** 506-511.

Of surgical interest only.—A. R. T.

**(THYROID) Thyroidism and Graves' disease as a form of traumatic neurosis (Thyreoidismus und Morbus Basedowii als eine Form der traumatischen Neurose).** Pulay (E.), Ztschr. f. klin. Med. (Berlin), 1919, **88,** 87.

According to the author Graves' disease is a form of increased irritability of the sympathetic system. But the increased irritability does not alone cause Graves' disease unless the patient has also a "status degenerativus" and unless there occurs also a special stimulation of the sympathic (psychical, traumatic, or infectious). This stimulation gives rise to the beginning of the disease. It is not true that the cause of the disease is abnormal functioning of the thyroid. The thyroid malfunction is, rather, a result merely of augmented sympathetic activity, as are the many other Graves' symptoms. No value is to be attached to various theories which ascribe a primary etiologic role in the disease to the thymus or the pancreas.

—J. K.

**THYROID therapy in skin diseases.** Pulay (E.), Therap. Monatshefte, 1919, **33,** 115.

A large number of dermatological conditions have been correlated with disturbances in thyroid function. Among these are erythema, hyperhidrosis, alopecia, atrophy of nails, and especially scleroderma. Administration of thyroid substance has been advocated in these cases. In the author's experience there is no specific or favorable result noted after such therapy.—Chem. Abst.

**(THYROID-PARATHYROID-ADRENAL) The role of the thyroid-parathyroid apparatus in uremia (Du role de l'association thyro-parathyroidienne dans l'uremie).** Remond (A.) and Minvielle, Bull. Acad. de Méd. (Paris), 1917, **77**, 504-507.

In an effort to study the mutual interrelationship between the thyroid, parathyroid and kidney, three series of experiments were performed: (1) nephrectomy, (2) nephrectomy with thyroidectomy, (3) thyro-parathyroidectomy with nephrectomy. It was found that survival of animals was the same in simple nephrectomy as in thyro-parathyroidectomy with nephrectomy, while in thyroidectomy with nephrectomy the survival was about half that in the other two series. The urea content of the blood was essentially the same in the first and third series, but in the second, the urea was much decreased while the chlorides were slightly increased. Summary:

| | Nephrectomy | Thyroid-nephrectomy | Thyro-parathyroid-nephrectomy |
|---|---|---|---|
| Survival in hours..... | 77 | 34 | 68 |
| Urea in blood, per liter | 5.97 | 1.99 | 5.69 |
| Chloride, per liter..... | 7.37 | 8.22 | 7.31 |

Thus, the removal of the parathyroid glands delays the early onset of intoxication occurring in the removal of kidneys and thyroids. In this the authors see an inhibitory action on the adrenal glands. Removal of thyroids with the kidneys has but little effect on the adrenal glands, while after removal of the parathyroids the adrenal appears to have been intensely active.—A. L. T.

**(THYROID) Two cases of nephritic exophthalmos (Deux cas d'exophtalmie néphrétique).** Rondopoulo (P. J.), Bull. Soc. Méd. des Hôp. (Paris), 1919, **43**, 4.

Two cases are described in which exophthalmos occurred in nephritics. That the exophthalmos was of thyroid origin was indicated by the presence of two of the Graefe, Möbius and Stellwag signs. The frequency of occurrence of exoph-

thalmos in nephritics was estimated to be about 3 per cent, occurring mostly in subacute or chronic nephritis.—A. L. T.

**(THYROID) Case of myxedema.** Saunders (A.), West London Med. J., 1917, **22,** 129.

A case of myxedema in a child of seven was shown. She had an enlarged thyroid at the age of two. At the age of five the left lobe was removed, after which the symptoms of myxedema developed. Her hair came out in patches and what was of additional interest were attacks of cyclic vomiting, which occurred every four months; simultaneously she became puffy over her entire body. Under persistent treatment with thyroid extract all her symptoms mentioned above vanished.—J. H. L.

**(THYROID) Exophthalmic goitre.** Schioetz (C.), Med. Rev. (Bergen), 1917, **34,** 1-20.

Report of a case of exophthalmic goitre, where the patient died after rapid loss of weight, vomiting, jaundice and albuminuria. Autopsy revealed an hyperplastic thyroid, thymus and anterior lobe of the pituitary; ovaries and pancreas were atrophic, liver and kidneys degenerated.

General remarks are offered as to the pathogenesis of the disease. The effect of thyroidin upon the protoplasm consisted of two phases: first, stimulation and later on destruction—analogous to the effect of certain inorganic poisons, e.g., mercury.—K. M.

**(THYROID )Riedel's goitre (Riedelscher strumitis).** Schloffer, Wiener. klin. Wchnschr., 1919, **32,** 930.

Description of a patient with an enormous goitre, hard as iron. No swollen lymph glands were detected. The clinical diagnosis "strumitis" (in the form described by Riedel) was confirmed by histological examination.—J. K.

**THYROID gland, Influence of the—upon metabolism. I. Carbohydrates.** Sekita (N.), Tokyo Igakukai Zisshi, 1918, **32,** 1-49; Jap. Med. Lit., 1919, **4,** 34.

From a study of thyroid functions, adrenaline glucosuria, and their relationship, the conclusion is drawn that the influence of the thyroid on carbohydrate metabolism has not been proved.—Chem. Abst., **13,** 2070.

**(THYROID) Operation for thyroid tumor.** Sherrill (J. G.), Ky. Med. J. (Bowling Green), 1919, **17,** 323-325.

Case report.—H. W.

**(THYROID) Trauma and Graves' disease (Trauma en Morbus Basedowii),** Simons (A.), Tijdschr. v. Ongevallen-Geneeskunde (Amsterdam), 1919, **4,** 247.

Description of two cases: 1st. A man fell with the abdomen against an engine. Twelve years before the accident he had been suffering from a Graves' disease which had disappeared after treatment. After this accident an acute Graves' disease developed. Some weeks after this he developed psychosis and died. The author believes that the trauma had an influence on the parasympathetic and sympathic systems and that the disease is caused by a disturbed equilibrium between these two systems. 2nd. A man fell in the water and developed, a fortnight later, acute Graves' disease. The patient died of cachexia. Autopsy showed a large thyroid with only a little colloid and status thymicus (large thymus and narrow aorta).

J. K.

**(THYROID) A brief study of goitre based on 1000 cases operated upon.** Sloan (E. P.), Ill. Med. J. (Chgo.), 1919, **35,** 226-227.

Summarizes the results with special reference to the onset of symptoms, age, sex, etc. Nothing new.—L. F. W.

**THYROID gland, The function of the—in relation to infections.** Sohmer (A. E.), St. Paul M. J. (St. Paul, Minn.), 1917, **19,** 297-301.

The author calls attention to the various known thyroid functions, developmental and metabolic. He cites experimental and clinical evidence that thyroid secretion has bacteriolytic and anti-toxic properties. He lays stress on the thyroid enlargement accompanying chronic infections, and concludes that it is only a step from this chronic irritation of the gland to the formation of a goiter with elaboration of toxic secretions.—A. R. T.

**(THYROID) Familial exophthalmic goitre.** Souques and Lermoyez (J.), Rev. Neurol. (Paris), 1919, **26,** 20-26.

Souques and Lermoyez relate that in the family described there have been seven cases of exophthalmic goitre among the sixteen members of the family in three generations. They give illustrations of the four members they have personally examined. The tendency seemed to be transmittd by the males.

There were no signs of inherited syphilis; the trouble must be some inherited predisposition rendering the thyroid peculiarly susceptible to diverse infections and intoxications. They list the few similar familial cases on record. In one, dating from 1884, eleven of the sixteen members of the family had developed exophthalmic goitre.—J. Am. M. Assn., **73**, 799.

**THYROID treatment of alopecia areata.** Strandberg (J.), Acta Medica Scandinavica (Stockholm), 1919, **52,** 165-176.

Strandberg now has a record of nine cases in which endocrine disturbances seemed to be responsible for malignant patches of alopecia. All were in men except three, but there was nothing to indicate positively endocrine disturbance. Two of the patients had dementia precox and one signs of syphilis. Thyroid treatment was applied in every case, but only briefly in two; in three of the cases the hair grew again under the thyroid treatment. In one man with dementia praecox the hair began to grow in as the mental condition improved. One woman who was not benefited by the thyroid had her hair drop out again during a pregnancy, and also when menstruation returned. The article is in German.—J. Am. M. Assn., **73,** 1736.

**(THYROID) A new ocular muscle symptom in exophthalmic goitre.** Suker (G. F.), J. Am. Med. Assn. (Chgo.), 1917, **68,** 1255.

"After extreme lateral rotation of the eyes, with fixation on an object at this point maintained for a second or two, on attempting to follow this fixation point as it is rapidly swung into the median line, one of the eyes fails to follow the other in a complementary manner into proper convergence. An apparent divergent strabismus is momentarily manifest." (Quoted.)

**(THYROID) An urgent tracheotomy (Een spoed-tracheotomie).** von der Tak (H.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1919, **63,** (II), 1448.

In a case of malignant goitre a very acute attack of dyspnea made immediate tracheotomy necessary.—J. K.

**(THYROID) Chagas' disease in Venezuela.** Tejera (E.), Gaceta Méd. de Caracas, Venezuela, 1919, **26,** 103.

Tejera presents conclusive evidence that the trypanosome thyroiditis described by Chagas in 1907 as common in children

in certain parts of Brazil prevails also in Venezuela. He reports two cases, in an infant and a boy of 2, belonging to the states of Trujillo and Zulia. His extensive study of the subject has demonstrated further that it is transmitted by a different insect from the one responsible for it in Brazil, Lamus (Conorhinos) megistus, as this does not seem to occur in Venezuela. The bug responsible for the transmission in Venezuela is Rhodnius prolixus Stal, as he determined by extensive experimental research and these clinical experiences. These insects in nature may harbor Trypanosoma cruzi. The insects are called by various names, pito, chupon, quipito, chinche de monte and chipo. It is a night-biting insect of the reduvidae family. Some specimens sent to Paris in 1913 from Venezuela were artificially infected by feeding them with Trypanosoma cruzi sent from Bahia, Brazil. Rincones presented Tjera's report sent from the laboratory of the Caribbean Petroleum Company at Mene Grande, and he added that a few years ago he urged research in Venezuela to find whether this American trypanosomiasis was restricted to Brazil alone. Tejera mentions in conclusion that, as goitre seems to be endemic in the Santander district in Colombia, Chagas' disease probably could be discovered there also. He was examining the rhodnius for Leishman bodies, in a study of American leishmaniosis, when he was surprised by the discovery in them of Trypanosoma cruzi of Chagas' disease. But his clinical cases of the latter came from a different district, and he found the trypanosome likewise in specimens of rhodnius from the environment of the patients. Rats, cats, monkeys and other animals inoculated from the insects developed the trypanosomes in large numbers in the blood. Ayala added that Tejera's research seems to exculpate the drinking water in respect to endemic goitre. He appealed further for research to decide whether there may not be some plant which serves as a host for the trypanosome like the euphorbia for the leptomonas (Iturbe), suggesting some zoological affinity between plants, Leishman bodies and trypanosomes.—J. Am. M. Assn., **73**, 565.

**(THYROID) Hyperthyroidism in influenza.** Todd (A. T.), Lancet (Lond.), 1919 (ii), 733-734.

Among 1500 cases of influenza 16 cases of hyperthyroidism developed. In all but one fatal case it appeared during convalescence. The onset was sudden in all cases.—L. G. K.

**(THYROID) Relation between water-supply and goitre.** Tolman (Mayo), Eng. News-Record, 1919, **83**, 516.

The cause of goitre is unknown, but has frequently been laid at the door of the water supply. T. claims that volcanic formations, the crystaline rocks of the Archaic period, and all deposits laid down in fresh water are free from goitre-producing characteristics. In the United States the greatest endemicity is found in Paleozoic areas. An estimate is made of 12,000 cases of goitre in West Virginia.—Chem. Abst., **13,** 3228.

**(THYROID) The psycho-neurotic syndrome of hyperthroidism.** Woodbury (M. S.), J. Nerv. & Ment. Dis. (N. Y.), 1918, **47,** 401-410; Clifton Med. Bull. (Clifton Springs), 1918, —, 18-23.

An excellent review and bibliography of the nervous and mental symptoms occurring in the course of Graves' disease. The author concludes that there is no distinct thyrotoxic psychosis, but that certain well-defined neurotic and psychotic symptoms arise in well-defined thyrotoxic cases. In the exophthalmic toxic cases, these symptoms are of the overcerebration and overstimulation type, dependent upon (1) cerebral hyperemia, (2) thyrotoxicosis per se, (3) toxicity from the increased waste products of metabolism. In the non-exophthalmic toxic cases, the mental picture is rather one of depression minus delusions. The latter cases comprise the adenomatous type of goitre and run a more sluggish course. They are distinguishable from non-endocrine neurasthenoid states by means of studies of the basal metabolism and the adrenin chloride test of Goetsch.—A. R. T.

**(THYROID) Iodin content of human thyroid glands (Sur la teneur en iode du corps thyroide de l'homme).** Zunz (E.), Réunion soc. belge biol., 1919, 22 Fév., 894-895.

The iodin content of the thyroid glands of normal human subjects, 21 to 34 years of age—men killed in war—was determined. In the majority of cases the range was 1.5 to 3 mgm. of iodin per gram of dry gland, or 0.46 to 0.84 mgm. per gm. of moist gland. The entire gland contained from 3.15 to 44.49 mgm., averaging 15.53 mgm. Diminution of the iodine content was noted in cases of bronchopneumonia.—Physiol. Abst., **4,** 338.

**(VAGOTONIA) Ueber Vagotonie und Sympathikotonie.** Klieneberger (C.), Berliner klin. Wchnschr., 1919, **56,** 719.

No new data. Cases of vagotonia, as described by Eppinger and Hess are very rare. The theory of vagotonia is very interesting, but it is only a theory. A great part of the liter-

ature on this subject shows a lack of critical sense and of pharmacological and physiological knowledge.—J. K.

**(VAGOTONIA) Ulcer of the stomach and autonomic nervous system (Ulcus pepticum und vegatitives Nervensystem).** Lehmann (G.), Berl. klin. Wchnschr., 1919, **56**, 772.

The author tried to find whether there is a relation betweel vagotonia and ulcers of the stomach. He found that the theory that the vagus and sympathic are antagonists is certainly not true. Most patients who are very sensitive to adrenalin are just as much so to pilocarpine. In modern literature we often read that patients with ulcers of the stomach show symptoms of vagotonia. The author could not confirm this. It is, however, true that such patients may show a disturbed function of their involuntary nervous system, but this is rare. In these cases the author believes that the ulcer is the cause of the change in the nervous system (through hemorrhage, under-feeding, etc.) The theory that ulcers of the stomach are caused by an abnormal function of the nervous system has never been proved and is not probable. Approximately 80 per cent of patients with ulcers show no symptoms whatever of so-called vagotonia. The clinical value of the word "vagotonia" is very small.—J. K.

The abstracts in this number have been prepared by the staff assisted by:

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With the permission of the editors, certain abstracts have been quoted from "Physiological Abstracts," "Chemical Abstracts" and "Surgery, Gynecology and Obstretrics."

## ELMER RAY HOSKINS

It is with much regret that we are called upon to record in these pages the decease of Professor Elmer Ray Hoskins, at Minneapolis, Minn., on January 30, 1920.

Professor Hoskins has been connected with our Association and ENDOCRINOLOGY since 1917, during the larger part of which time he has served as a Collaborator on the Editorial Staff.

As will be noted, Professor Hoskins and his wife prepared the leading paper in this number of ENDOCRINOLOGY, together with several items in the Abstract Department.

We take this means of expressing our sincere sympathy to his wife and other surviving members of his family in this, their great bereavement. We share with them the great loss which they have sustained.

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